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Contents on Inside Cover

American Heart Journal

CONTENTS FOR NOVEMBER, 1948

Original Communications

The Amount of Digitoxin (Digitaline Nativelle) Required for Adequate Digitalization. Harold J. Stewart, M.D., and Abbott A. Newman, M.D., New York, N. Y. 641

Continuous Observations of the Arterial Oxygen Saturation at Rest and During Exercise in Congenital Heart Disease. George E. Montgomery, Jr., M.D., Earl H. Wood, M.D., Ph.D., Howard B. Burchell, M.D., Thomas J. Dry, M.D., Robert L. Parker, M.D., and H. Frederic Helmholz, Jr., M.D. With the Technical Assistance of L. Cronin, Rochester, Minn. 668

Coronary Artery Disease in Men Eighteen to Thirty-Nine Years of Age. Wallace M. Yater, M.D., Washington, D. C., Aaron H. Traum, M.D., Silver Spring, Md., Wilson G. Brown, M.D., St. Louis, Mo., Richard P. Fitzgerald, M.D., First Lieutenant, M.C., A.U.S., Murray A. Geisler, M.A., Arlington, Va., and Blanche B. Wilcox, Ph.D., Washington, D. C. 683

A Clinical Evaluation of Veratrum Viride in the Treatment of Essential Hypertension. Edward D. Freis, M.D., and Joseph R. Stanton, M.D., Boston, Mass. 723

The Effect of Posture Upon Axis Deviation in Human Bundle Branch Block. A. Morgan Jones, M.R.C.P., Manchester, England, and Harold Feil, M.D., Cleveland, Ohio 739

Determination of the Levo- and Dextrocardiogram. Marcel Segers, M.D., Brussels, Belgium 751

Further Experience With Thromboangiitis Obliterans in Women. Samuel Silbert, M.D., New York, N. Y. 757

Clinical Reports

A Case of Paradoxical Embolism. Colin A. Ross, M.D., and P. H. Sprague, M.D., Edmonton, Alberta, Canada 772

Extreme Bradycardia. Joseph C. Doane, M.D., and Sidney O. Krasnoff, M.D., Philadelphia, Pa. 777

Abstracts and Reviews

Selected Abstracts 783

American Heart Association, Inc. 796

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American Heart Journal

VOL. 36 NOVEMBER, 1948 No. 5

Original Communications

THE AMOUNT OF DIGITOXIN (DIGITALINE NATIVELLE) REQUIRED FOR ADEQUATE DIGITALIZATION

HAROLD J. STEWART, M.D., AND ABBOTT A. NEWMAN, M.D.*
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IN RECENT years, digitalis glycosides have been substituted for the whole digitalis leaf in the treatment of circulatory disorders. Although observations on the effects of these drugs are now extensive, important questions concerning their optimal dosage and method of administration have not been finally answered.

Using the effect of the drug on the ventricular rate of auricular fibrillation as a criterion, Gold and his associates have presented charts indicating that digitoxin and the whole leaf are absorbed from the gastrointestinal tract at approximately parallel rates.[1-3] They also have reproduced charts showing that the slowing of ventricular rate is slightly more rapid when digitoxin is given intravenously than when given by mouth, but the optimal effect is observed at approximately the same time in each.[1-4] They reproduced one chart, however, (Patient B. S.[1]) in which the slowing proceeded at approximately the same rate in both routes of administration. One would infer that the effect of the whole leaf, administered by mouth, may be as rapid as that obtained from the use of digitoxin intravenously. The authors believe that digitoxin is more completely absorbed from the gastrointestinal tract than the whole leaf since it takes a larger amount of the whole leaf to induce a comparable effect.[1,2] They state: "When one gives a dose of digitalis by mouth in the form of the leaf or of the tincture, only about one-fifth is absorbed. The remaining four-fifths contributes nothing to the therapeutic action."[2]

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Gold and his co-workers further maintain that 1.0 mg. of digitoxin is equivalent to 1.0 Gm. of powdered leaf.[1,4] They state that the average dose of Digitaline Nativelle for full therapeutic digitalization is 1.2 mg.[1,2,4-6] which may be compared with 1.8 Gm. which we found to be the average digitalizing dose of the whole leaf (New York Heart Association preparation).[6-8] They state that 1.2 mg. is the average full digitalizing dose[5] without qualification, but in other publications indicate that there are some patients who may require more or need less.[1,2] Examination of their data does not reveal clearly the derivation of their average digitalizing dose nor do they make a definite statement of their criteria for full therapeutic digitalization. In a paper[1, p. 188] in which they discuss the use of the slowing of the ventricular rate as a guide to digitalis effect, they do not make a definite statement about what degree of slowing is to be the objective. From the chart[1, Fig. 2] which is a composite of data relating to several patients with varying degrees of slowing by digitoxin, it is not possible to determine how many were adequately digitalized by 1.25 milligrams. Indeed, Gold states: "We have not made a distribution or a scatter curve of the therapeutic effects of the 1.2 mg. given at one time. We have made the scatter curve with the maintenance dose of 0.2 mg. which we have just discussed. We have not done this yet with the single dose digitalization."[6, p. 1680] Again, he says, "While we have not determined precisely what proportion of patients are fully digitalized by the 1.2 mg. dose given at one time, we do have some information about that dose since it produces an effect equal to 1.2 Gm. of digitalis."[6] Gold and his associates state categorically that single dose digitalization with 1.25 mg. of digitoxin is a safe and satisfactory procedure.[1,2,4,5] On the other hand, De Graff[9] finds that this amount digitalized less than 20 per cent of his patients who were being digitalized for the first time. He considers the average digitalizing dose to be 2.2 milligrams. Katz and Wise[10] did not assay the amount of digitoxin required for full digitalization; they state, however, that after 1.2 mg. were given it was necessary sometimes to follow with further smaller doses before adequate digitalization was obtained. They did not give their criteria for digitalization.

With such conflicting statements, one must remain in doubt concerning optimal dosage and indeed may question whether Gold's repetition of the statement that 1.2 mg. is the average full therapeutic digitalizing dose may not be harmful to patients who require more for complete digitalization.

There has also been much discussion as to the equivalence of single and divided doses of digitoxin. In our experience with the digitalis leaf administered orally, it was found that safe and satisfactory digitalization could be obtained with 1.8 Gm. (New York Heart Association preparation) in the average patient either in divided doses[11,12] or, when there was urgency and the strength of the preparation was known, by a single large dose.[13] Translation of this experience to the use of digitoxin has not been satisfactorily demonstrated.

In our studies with digitoxin* we chose patients with auricular fibrillation because the slowing of the ventricular rate is a satisfactory guide to digitalis effect. We attempted to reduce the rapid ventricular rates in auricular fibrilla-

*Digitalline Nativelle was used in this study.

tion in twenty-four hours to around 70 to 75 per minute, which is the rate we consider the optimal one for therapeutic purposes,[8] a matter concerning which there is general agreement.

Levine[14, p.274] states with respect to the use of digitalis in auricular fibrillation, "The hope is to slow the apex rate to 60 or 70 per minute if possible, without producing any ill effects." Further, "If the heart rate has slowed to 70 the dose is reduced to 0.1 Gm. a day." He also states,[14, p.286] "A heart that is beating irregularily at a rate of 60 to 70 can be about as efficient as if it were beating regularily at a rate of 70 to 80. In fact a slow irregular rate may maintain a better circulation than a rapid regular one. It was occasionally found that in the presence of stubborn congestive heart failure when the regular rate was 100 or more, improvement might first become manifest only after auricular fibrillation developed. What would happen was that digitalis that was given failed to slow the regular rhythm and when auricular fibrillation began the drug slowed the ventricular rate to 60 or 70 and congestion began to clear." White[15, pp. 770 and 771] points out that slowing the ventricular rate in auricular fibrillation from 160 to 60 per minute "means sparing the heart muscle an unnecessary and often ineffective amount of labor consisting of 6,000 beats an hour or well over 100,000 beats a day. Even a reduction of but 50 beats, which is common, say from a rate of 120 to one of 70, means an omission of 72,000 contractions a day." Gold,[5] in speaking of digitalizing, says, "The decline of the ventricular rate to about 70 per minute is the most satisfactory guide." Gold[3, p. 552] also states in discussing the use of digitalis in auricular fibrillation, "The desired effect is to maintain a rate of 70 per minute." Levy[6, p. 1677] makes the following statement in discussing maintenance dosage of Digitaline Nativelle: "We have seen patients with auricular fibrillation who could be maintained at the proper rate, and by 'proper rate' I mean one that does not rise above 80 under ordinary exertion with as little as 0.1 mg. every second day."

It has been our experience that the clinical dosage of digitalis required for full therapeutic digitalization can be established on patients with rapid auricular fibrillation. The amount of the drug, which by complete absorption in twenty-four hours will slow the ventricular rate to around 70 to 75 per minute, has been found in our experience to be the optimal therapeutic amount in the clinical use of the drug. This has appeared to be approximately the same for all adult patients, irrespective of body weight. The amount of the preparation which accomplished this is then found to achieve therapeutic digitalization in patients with normal sinus rhythm in whom there is not the guide of heart rate as in patients with auricular fibrillation.[8,11,12] Spreading the amount of the drug to be given for full digitalization over a period of eighteen hours does not increase the amount required for digitalization, because excretion during the first twenty-four hours can be neglected for clinical purposes or at most could only make the difference of one daily maintenance.[11] We are of the opinion that digitalization can and should be accomplished without nausea and vomiting.

Our investigations concerned twenty-six patients and included two phases: (1) The hospital records of all patients from 1942 to 1946 having auricular fibrillation who received digitoxin were reviewed to ascertain the effect of this

drug on ventricular rate, and (2) observations were made on the amount of digitoxin required, according to our standards, to produce full digitalization in patients with auricular fibrillation. Many patients who received the drug were excluded from the analysis for the following reasons: (1) the use of other drugs, (2) the onset of complications, (3) the simultaneous use of digitalis and potassium iodide in hyperthyroid patients, and (4) inadequate control periods.

The following observations on digitoxin were made: (1) The effect of digitoxin, 1.2 mg., given in one intravenous dose, was observed in four patients (Cases 1, 2, 3, and 4). (2) The effect of digitoxin, 1.2 mg., given in one oral dose, was observed in four patients (Cases 5, 6, 7, and 8). (3) The effect of digitoxin, 1.2 mg., as the initial dose, followed by supplementary amounts to complete digitalization, was observed in six patients (Cases 3, 4, 5, 6, 7, and 8). (4) The effect of digitoxin, 1.8 mg., in a single oral dose, was recorded in four patients (Cases 9, 10, 11, and 12). (5) The effect of digitoxin, 1.8 mg., as the initial dose, followed by supplementary amounts to complete digitalization, was observed in two patients (Cases 11 and 12). (6) The effect of digitalization with digitoxin in smaller or divided amounts was observed in ten patients (Cases 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22). (7) Observation was made of amounts of digitoxin to achieve digitalization in four patients (Cases 23, 24, 25, and 26) with hyperthyroidism. (8) An attempt was made to ascertain the maintenance dosage of digitoxin. (9) An attempt was made to discover if comparable digitalization occurred when the equal doses of the drug were given orally and intravenously.

In patients in whom the amount given in one dose or in divided doses during the first day was inadequate to reduce the ventricular rate to 70 to 75 per minute, and to whom additional amounts were given on subsequent days to achieve satisfactory digitalization, we have calculated the digitalizing amount, if all had been given on the first day, in the following manner. Experience with the whole leaf has shown that during the first day and with equal total amounts of drug the degree of digitalization is essentially the same with single or with broken dosage. For practical purposes excretion on this day can be neglected. After satisfactory digitalization was attained we tried to assay the maintenance amount in the patient to keep the ventricular rate at the level of 70 to 75 per minute. From the total amount necessary to achieve digitalization and also maintenance over x days is subtracted the maintenance requirement over $x - 1$ day, to give the amount which should have been given on the first day to secure the required level of digitalization for that patient; this is called the calculated digitalization dose for the patient. We have reason to believe that this is valid for the following reasons: (1) The amount corresponds closely with the amount which was required when given in twenty-four hours. (2) We have found that in the digitalization of ambulatory patients with the whole leaf we can attain digitalization in a selected and allotted time if we give over that period the digitalizing amount (1.8 Gm.), plus the total maintenance amount to take care of excretion.[8] We are aware that a patient can be digitalized over a long period by being given small amounts daily, a certain amount of this being retained toward digitalization.

PROCEDURE

On admission to the hospital, the patients were observed during a preliminary control period of two or more days of complete bed rest on a low-salt diet. The fluid intake was fixed, the amount depending on whether or not cardiac failure was present. Daily observations were made on the cardiac and general clinical status of the patient. Apical and radial rates were counted every four hours. The weight was obtained daily before breakfast. Diuretics and other treatment deemed necessary were allowed during this period, but digitalis in any form was withheld. If it was suspected that digitalis had been given at any time during the two weeks before admission, the control period was prolonged for two to three weeks after the last dose to provide for elimination of the drug. In several instances the control period had to be terminated early where indications for the prompt administration of digitalis arose, such as a continued rise in heart rate and increase in signs of heart failure.

After stabilization of the patient's clinical status, the dose of digitoxin which had been decided upon was given. The need for additional doses during the first twenty-four hours was ascertained by observation of the patient several times daily. In order to calculate the pulse deficits, apical and radial pulse rates were recorded every two hours except at night during the first day of digitalization, and every four hours thereafter. An electrocardiogram was taken before digitalization, repeated several hours after the initial dose, again the following day, and thereafter as indicated. The patients were kept at bed rest throughout the period of digitalization and the period of ascertaining the maintenance requirements. Signs of digitalis intoxication were watched for.

OBSERVATIONS

Twelve patients (Table I) exhibiting auricular fibrillation who were given digitoxin are briefly presented to illustrate the effects obtained with certain amounts of the drug. In Cases 1, 3, and 4, digitoxin, 1.2 mg., was given in a single intravenous dose, with supplementary amounts to complete digitalization. In Cases 5, 6, 7, and 8, 1.2 mg. was given in a single oral dose and added amounts given to complete digitalization. In Cases 9, 10, 11, and 12, digitoxin, 1.8 mg., was given in one oral dose, with supplementary doses when digitalization had not been completed by this amount. Case 13 illustrates a patient who received 0.6 mg. intravenously, followed by 0.4 mg. by mouth, several hours later. A total of 2.8 mg. was ultimately required to digitalize this patient.

CASE 1 (394086) (Fig. 1, Table I).—A 45-year-old white woman, known to have had rheumatic heart disease since the age of 23, experienced palpitation, tachycardia, and a dull, aching sensation in the precordium ten days before admission to the hospital. Her weight was 59 kilograms. There was no dyspnea or cyanosis. A few fine râles were heard at both lung bases. The heart was enlarged to the left. There were typical signs of mitral stenosis and insufficiency. There was no edema or ascites. Auricular fibrillation with a ventricular rate of 125 per minute was present.

The patient was kept at rest in bed on a regular ward diet and fluids allowed as desired. After a four-day control period, when the heart rate was 120 per minute, digitoxin, 1.2 mg., was given in a single intravenous dose (Fig. 1). Twenty-four hours afterward the heart rate was 74 per minute. There were no symptoms of intoxication.

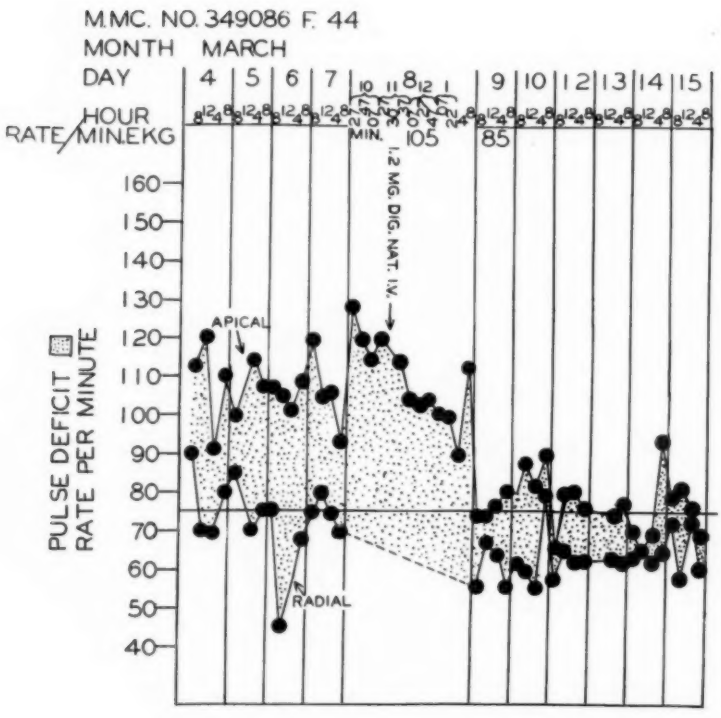

Fig. 1.—In this figure are shown data relating to Case 1, Patient M. Mc., to whom digitoxin, 1.2 mg., was given in one dose intravenously. In this chart, as well as in those which follow, the upper series of connected dots represent the apical heart rate and the lower series of dots, the radial rate, with stippled area indicating the pulse deficit. On the day digitalis was given, the minutes as well as the hours are recorded.

In this patient with a not too rapid ventricular rate, 1.2 mg. of digitoxin achieved adequate digitalization and slowed the heart rate to the sought-for level of 75 per minute. She was not given maintenance amounts of the drug, for we wished to follow the effect of this single dose.

CASE 3 (28212) (Fig. 2, Table I).—A 35-year-old white housewife was admitted to hospital on Sept. 17, 1945, because of palpitation, dyspnea, and weakness of one month's duration. She had a history of rheumatic fever at 18 years of age and had been followed in the New York Hospital Cardiac Clinic since 1933. Physical examination revealed an enlarged heart with the characteristic murmurs of mitral insufficiency and stenosis. The rhythm was auricular fibrillation, the apical rate being 150 per minute, and the radial, 85 per minute. There was no edema. Her weight was 58.1 kilograms.

The patient was observed for six days while at bed rest. Fluids were limited to 1,500 cubic centimeters. During this time she lost 3.1 kilograms in weight and the cardiac rate was recorded between 110 and 150 per minute.

On the seventh hospital day, digitoxin 1.2 mg. was administered intravenously in one dose. This resulted in a fall in cardiac rate from 146 per minute to 90 per minute in two hours (Fig. 2). No symptoms of intoxication occurred. Twenty-four hours after the initial dose, the cardiac rate was 86 per minute with a pulse deficit of about 10 per minute. Forty-eight hours after the initial dose the heart rate had returned to 90 per minute and seventy-two hours after the initial

dose it was still at this figure. It was apparent that 1.2 mg. of the drug, although given intravenously in one dose, did not achieve satisfactory digitalization according to our standards. Digitalization was then completed by supplementary small oral doses of 0.2 to 0.4 mg. daily. A total of 2.2 mg. was given over five days to reduce the cardiac rate to 75 per minute. Slight nausea but no other symptoms occurred after a total of 2.4 mg. had been given. The patient was subsequently given 0.2 mg. as the maintenance amount.

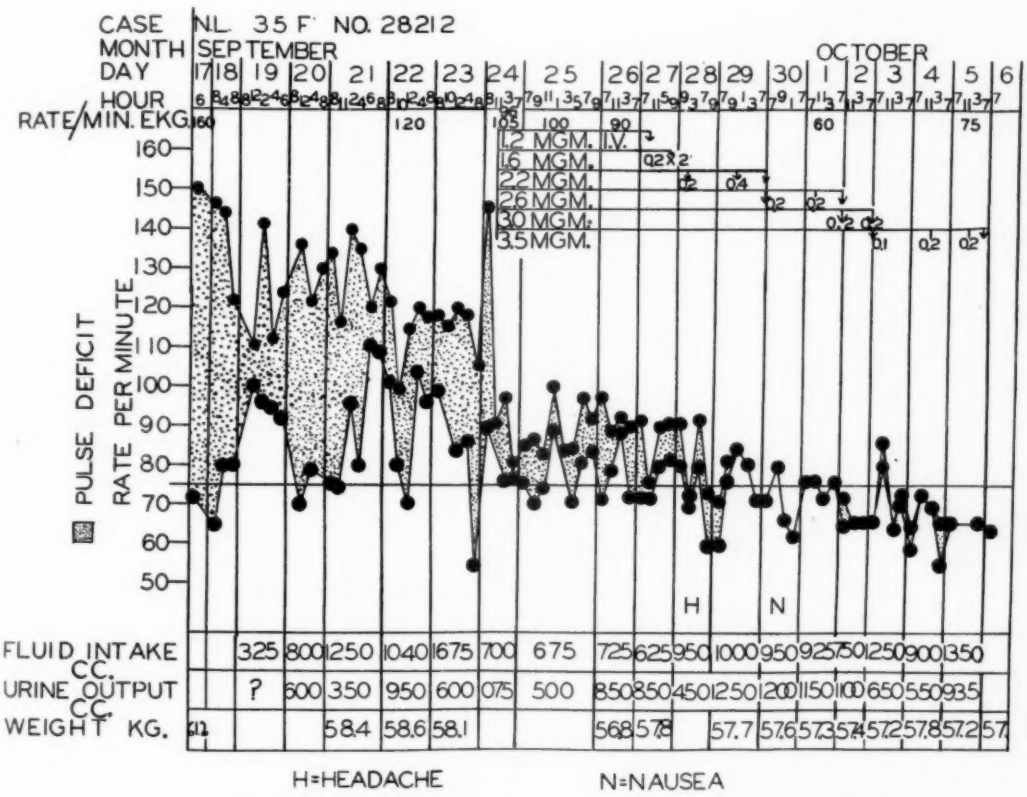

Fig. 2.—In this figure are shown data relating to Case 3, Patient N. L. Digitoxin, 1.2 mg., was given in an initial intravenous dose. Additional oral doses were given as indicated. In this chart and in those to follow, a vertical bar shows the time digitalis was first given. The amounts shown along this vertical line indicate the total amount of digitoxin which the patient received from the beginning to the end of the horizontal line with an arrow at the end. The time at which the additional amounts of drug were given is indicated by arrows from the horizontal line. In this manner of charting, the total amount of digitalis up to any one day and its distribution are readily apparent.

It is apparent that 0.2 mg. as a maintenance amount was too much since the heart rate continued to fall (Fig. 2). It is also apparent that 1.2 mg. given intravenously in one dose was insufficient to digitalize this patient, three days being allowed to observe its effects; that 1.6 mg. was inadequate; that 1.8 mg. was likewise insufficient; and that not until a total of 2.2 mg. had been given did the heart rate fall to a satisfactory level. It is estimated that 1.8 mg. would have been adequate if given in the first twenty-four hours (see p. 644), allowing the rest for maintenance over this period.

TABLE I. DATA RELATING TO THE AMOUNT OF DIGITALINE NATIVELLE RE

CASE	INITIALS	HISTORY NO.	ETIOL. DIAGNOSIS	ANAT. DIAGNOSIS	INITIAL DOSE (SINGLE) (MG.)	ROUTE DRUG GIVEN	DIVIDED DOSE SCHEME
1	M. McC.	349086	R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
2	N. K.	381135	H.A.S.H.D.	(E.H.)	1.2	I.V.	
3	N. L.	28212	R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
4	M. A.	84878	Hy. + R.H.D.	M.S.M.I.E.H.	1.2	I.V.	
5	W. L.	137050	A.S.H.D.	Myo.Fibr.	1.2	oral	
6	M. StL.	115465	H.A.S.H.D.	(E.H.)	1.2	oral	
7	K. C.	430023	Undeter.	? Cor.Pul.	1.2	oral	
8	M. H.	249105	A.S.H.D.	M.Scl. + calc. and E.H.	1.2	oral	
9	H. W.	433820	R.H.D.	M.S.E.H.	1.8	oral	
10	N. S.	229324	Hy.H.D.	(E.H.)	1.8	oral	
11	H. R.	443670	A.S.H.D.	(E.H.)	1.8	oral	
12	M. F.	365004	H.A.S.H.D.	(E.H.)	1.8	oral	
13	J. McC.	428209	A.S.H.D.	(E.H.) C.A.D. C.O.Myo.Fibr.		0.6 I.V. 0.4 oral	0.6 I.V. 0.4 oral
14	S. H.	332032	Hy.H.D.	(E.H.)		oral	0.4, 0.4, 0.2, 0.2
15	A. R.	254403	Hy.H.D.	C.A.D. (cor.scl.) (E.H.)		oral	0.4 × 3 = 1.2
16	C. C.	219875	R.H.D.	M.S.M.I.A.S.A.I. E.H.		oral	0.2 × 7 = 1.4
17	E. M.	388084	R.H.D.	?M.S.M.I.A.S.A.I. E.H., B.B.B., C.A.D.		oral	0.2 × 6 = 1.2
18	A. P.	298234	H.A.S.H.D.	(E.H.)		oral	0.2, 0.1
19	A. H.	339998	H.A.S.H.D.	(E.H.)		oral	0.2 × 10 = 2.0
20	M. M.	19397	R.H.D.	(E.H.)M.S.M.I.A.I.		oral	
21	M. G.	376577	A.S.H.D.	(E.H.)		oral	0.5 + 0.3 + 0.2 + 0.2
22	L. S.	101768	R.H.D.	(?M.S.)M.I.E.H.		I.V.	0.4 + 0.8 I.V.
23	A. V.	423504	Hypth.A.S.H.D.	(E.H.)	1.2	oral	
24	G. O.	415472	Hypth.H.D.	(E.H.)	1.6	oral	
25	G. R.	426937	Hypth.H.D.		1.2	oral	
26	E. D.	441717	Hypth.A.S.H.D.	(E.H.)	1.2	oral	1.6 in 16 hrs.

R.H.D. = rheumatic heart disease; H.A.S.H.D. = Hypertensive arteriosclerotic heart disease; A.S. tension plus rheumatic heart disease; Hypth. = Hyperthyroid.

M.S. = mitral stenosis; M.I. = mitral insufficiency; A.S. = aortic stenosis; A.I. = aortic insuffi Cor.pul. = cor pumonale; C.O. = coronary occlusion.

I.V. = intravenously.

0 = none; + = yes; + to ++++ = degree.

CASE 4 (84878) (Fig. 3, Table I).—A 35-year-old white woman with known rheumatic heart disease who weighed 74.9 kilograms underwent bilateral lumbodorsal sympathectomy for essential hypertension on Dec. 5 and 17, 1945. The patient's course for the first forty-eight hours following the second operation was uneventful, but in the evening of the second postoperative day, the rhythm changed to auricular fibrillation with a ventricular rate of 130 per minute. There was no evidence of heart failure, and the patient was without symptoms.

It was decided to give 1.2 mg. of digitoxin intravenously in one dose at once (Fig. 3). Sixteen hours after this dose was given, the cardiac rate had only decreased to 94 per minute. There were no symptoms of intoxication. An additional oral dose of 0.4 mg. was given. This produced nausea and vomiting without affording full digitalization. An additional 0.2 mg. was given forty-eight hours after the initial dose, and the effect of a total 1.8 mg. was to slow the heart rate to

QUIRED TO DIGITALIZE TWENTY-SIX PATIENTS WITH AURICULAR FIBRILLATION

CASE	TOTAL DOSE TO DIGITALIZE IN TIME (COL. 11) (MG.)	INITIAL HEART RATE (MIN.)	FINAL HEART RATE (TIME OF TOTAL DOSE) (MIN.)	TIME REQUIRED TO SLOW RATE (HOURS)	ESTIMATED DIGITALIZING DOSE AFTER CORRECT. FOR AV. DAILY EXCRETION (MG.)	AV. DAILY MAINTENANCE DOSE (MG.)	DEGREE OF HEART FAILURE	WEIGHT (KG.)	TOXICITY FROM DIG.
1	1.2	128	76	24	1.2		0	59.0	
2	1.2	128	82	22			+	86.4	
3	2.2	146	72	120	1.8	0.1	0	58.1	+
4	1.8	130	74	72	1.7	0.1	0	73.9	+
5	2.2	145-120	74	60	2.0	0.1	0	50.4	+
6	3.3	150	76	168	2.4	0.1 - 0.2	++++	53.0	+
7	2.0	135	70	96	1.8	0.1 mg. q. 2 days	0	54.0	0
8	2.6	140	74	120	2.4	0.2	+++	40.0	+
9	1.8	140	70	12	1.8	0.1 - 0.2	0	58.4	?
10	5.0	136	75	15 days	2.9	0.1 - 0.2	++++	77.0	+
11	2.2	134	75	72	2.0	0.2	++	61.0	+
12	1.8	115	75	24	1.8	0.2	+++	38.2	0
13	2.8	128	74	156	2.1	0.1 - 0.2		?	0
14	3.6	136	76	176	2.2	0.1 - 0.2	++	75.0	
15	2.8	122	72	144	1.8	0.1 - 0.2	++	74.6	
16	1.8	126	76	84	1.6	>0.1	+	?	
17	2.3	143	76	144	1.7	0.1 - 0.2	0	59.5	
18	2.9	126	76	168	2.0	0.1 - 0.2	+++	52.0	
19	3.4	136	70	96	3.0	0.1	++	53.6	
20	2.3	210	72	39			+	74.0	
21	1.2	120	110	16			0	?	
22	1.2 (q.n.s.)	144	85-120	48		0.2	±	70.5	
23	3.4	142	75	96		0.1	0	45.3	
24	4.4	200	86	192		0.2	++++	58.0	
25	3.4	180	95	120			0	60.2	
26	1.6	120	82	24			0	38.6	

H.D. = Arteriosclerotic heart disease; HyH.D. = Hypertensive heart disease; Hy + R.H.D. = Hyperciency; E.H. = enlarged heart; C.A.D. = coronary artery disease; Myo.Fibr. = myocardial fibrosis;

between 70 and 80 per minute. Maintenance doses averaging 0.1 mg. daily were continued. Headache, anorexia, and blurring of vision occurred on the seventh day of digitalis therapy, when the heart rate was 70 per minute. A total of 1.8 mg. given in forty-eight hours was necessary in this case to achieve full digitalization.

It is apparent (1) that 1.2 mg. given intravenously in one dose did not achieve adequate digitalization, (2) that a total of 1.6 mg. did not slow the heart rate sufficiently, but caused nausea and vomiting, and (3) that 1.8 mg. in forty-eight hours reduced the ventricular rate to around 75 per minute. The average maintenance amount was 0.1 mg.; if this is subtracted from 1.8 mg. as the maintenance amount in the second twenty-four hours of digitalization, it appears that

around 1.7 mg. would have been adequate to slow the rate if given in twenty-four hours.

CASE 5 (137050) (Fig. 4, Table 1).—An 86-year-old white man was admitted to hospital on Oct. 1, 1945, because of severe chest pain the night before admission. The patient had been followed in the New York Hospital Cardiac Clinic since 1933. The diagnosis was arteriosclerotic heart disease with an enlarged heart, pulmonary fibrosis, and emphysema.

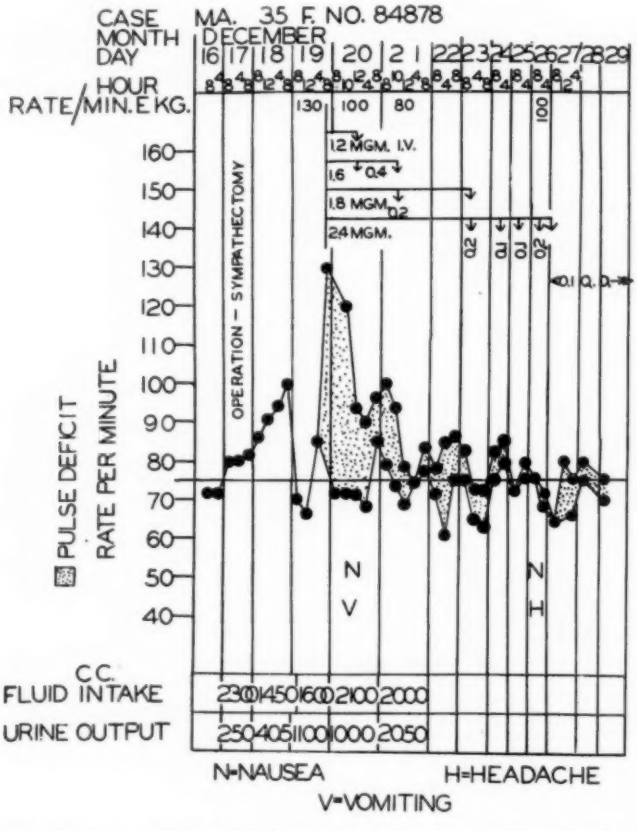

Fig. 3.—In this figure are shown data relating to Case 4, Patient M. A. Digitoxin, 1.2 mg., was given in an initial intravenous dose. Subsequent oral doses are shown.

There was no evidence of heart failure on admission. The blood pressure was 126/74. The lungs were clear. The heart was enlarged; auricular fibrillation with an apical rate of 140 per minute and a radial rate of 124 per minute were present. There was no edema. The patient weighed 50.4 kilograms.

The patient was observed for three days on a general diet and a limited fluid program without loss of weight. The apical heart rate fluctuated between 100 and 140 per minute with a pulse deficit ranging from 0 to 42 per minute. On the fourth hospital day, digitoxin 1.2 mg. was given in one oral dose (Fig. 4). This resulted in a fall in the cardiac rate from between 120 and 145 to 94 per minute in twelve hours and to 90 per minute in thirty-six hours. No symptoms of intoxication occurred. On the sixth hospital day, two days later, a total of 1.0 mg. of the drug was given in divided doses by mouth in an effort to complete digitalization. This induced nausea

The heart rate fell to 70 per minute. A total of 2.2 mg. of digitoxin in sixty hours was necessary for satisfactory digitalization. The patient was then given 0.1 mg. daily as the maintenance amount.

In this patient, 1.2 mg. by mouth in one dose in a man weighing only 50.4 kilograms was inadequate to achieve digitalization. The effect of this amount was observed during the following day. On the third day 1.0 mg. additional was given in divided doses and reduced the rate satisfactorily, making a total of 2.2 milligrams. This induced nausea. Since the average maintenance amount in this patient was 0.1 mg. daily, and 2.2 mg. was given over three days, if 0.1×2.0 is subtracted for the maintenance amount for the last two of these days, we arrive at 2.0 mg. as the digitalizing amount.

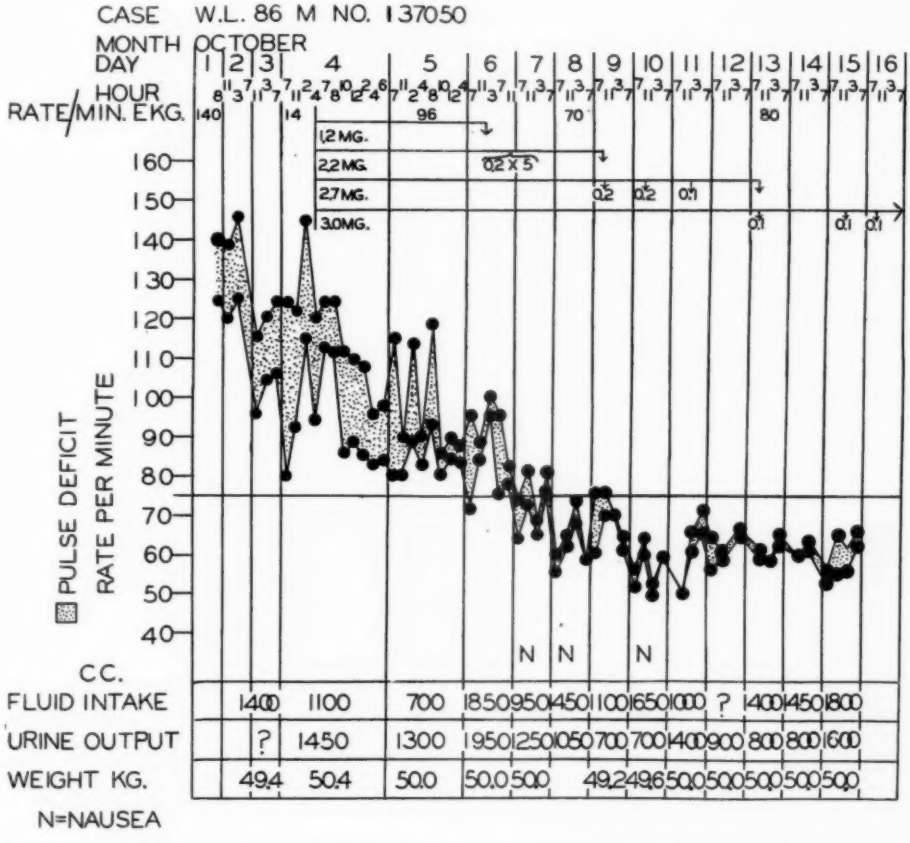

Fig. 4.—In this figure are shown data relating to Case 5, Patient W. L. Digitoxin, 1.2 mg., was given as an initial oral dose. Subsequent oral doses are shown.

Case 6 (115465) (Fig. 5, Table I).—A 76-year-old white woman was admitted to the hospital for the first time because of dyspnea, orthopnea, and swelling of the ankles. This was the first episode of cardiac decompensation. There was no previous history of rheumatic fever or hypertension. She weighed 53.0 kilograms. The neck veins were distended; she was moderately dyspneic and orthopneic. Moist râles were heard at both lung bases. The heart was enlarged to

the left. Auricular fibrillation was present with the ventricular rate of 150 per minute and radial rate of 126 per minute. The blood pressure was 190/120. The liver was enlarged and there was peripheral edema. The patient remained at bed rest for three days on a 3.0 Gm. salt diet and limited fluids. During this period the cardiac rate ranged between 114 and 150 per minute. The diagnosis was hypertensive and arteriosclerotic heart disease.

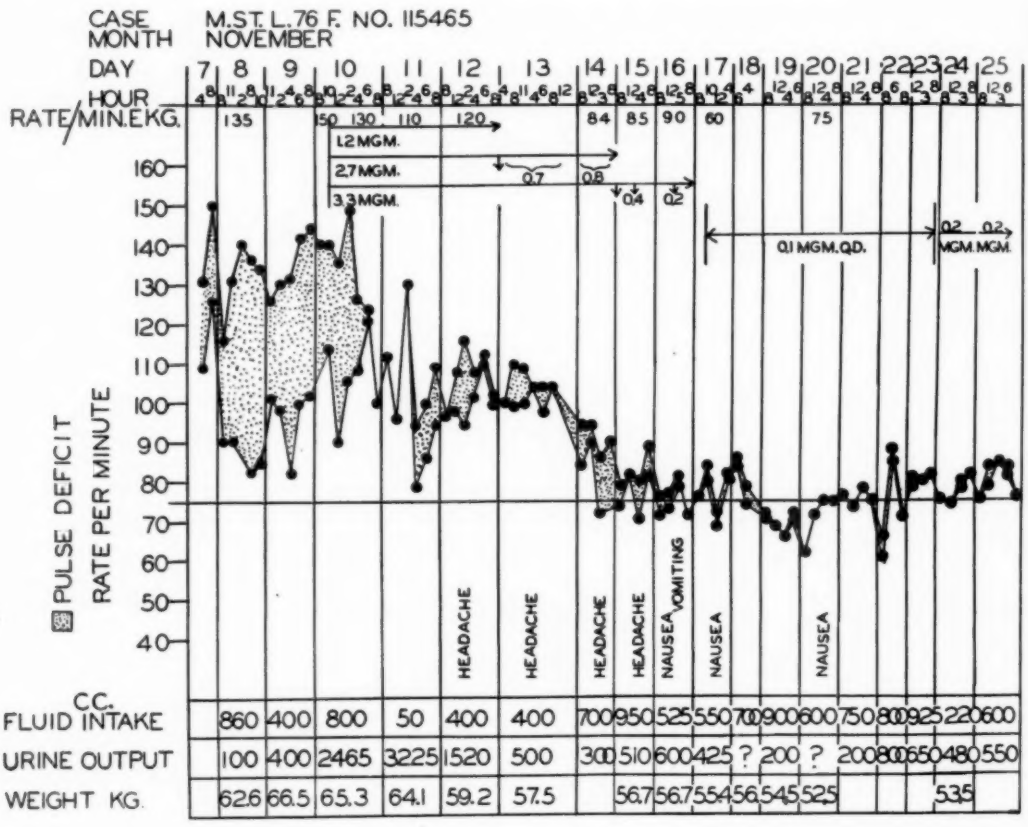

Fig. 5.—In this figure are shown data relating to Case 6, Patient M. St.L. Digitoxin, 1.2 mg., was given as an initial oral dose. Subsequent oral doses are shown.

On the fourth hospital day, digitoxin 1.2 mg., was given orally in one dose (Fig. 5). Twelve hours afterward the cardiac rate had fallen from 150 to 98 per minute. There were no symptoms of intoxication. Digitalis was not given for the next two days. During this time a weight loss of 4.9 kilograms occurred; slight edema remained and râles were still heard in the lungs. On the second day after the initial dose of digitoxin the patient complained of a slight headache, but the heart rate was 110 per minute. On the next day 0.7 mg. was given and 0.8 mg. on the following day, a total of 2.7 milligrams. Headache persisted, but no further symptoms of intoxication occurred. The heart rate fell to 90 per minute. In the following two days 0.6 mg. of digitoxin was given. A total of 3.3 mg. given in six days reduced the heart rate to 75 per minute. This produced nausea and vomiting. The patient was maintained for the next seven days on 0.1 mg. daily and was discharged on 0.2 mg. daily.

In this patient, weighing only 53.0 kilograms, 1.2 mg. in one dose by mouth was inadequate to achieve digitalization. The effect of this was observed for the two following days; the addition of 0.7 mg. and then 0.8 mg. on the fourth and fifth days, respectively, making a total of 2.7 mg., was not sufficient; not until 0.4 mg. and 0.2 mg. were given on the next two days, respectively, making a total of 3.3 mg. in seven days, was the rate reduced adequately. The maintenance amount in this patient was between 0.1 and 0.2 milligram. If the amount for six days' maintenance, 0.9 mg. (0.15 × 6), is subtracted from the total amount, we arrive at 2.4 mg. as the digitalizing amount for this patient if it had been given in twenty-four hours.

CASE 7 (430023) (Fig. 6, Table I).—A 55-year-old white housewife was admitted to hospital on Dec. 3, 1945, because of chills and fever, chest pain, and bloody sputum of one week's duration. This condition was associated with cough, dyspnea, and increasing orthopnea. Examination revealed an acutely ill woman who was dyspneic, orthopneic, and cyanotic. Her weight was 54.0 kilograms. Flatness, tubular breathing, and fine râles were present at the right lung base. The heart was enlarged. There was no edema. Auricular fibrillation with a ventricular rate of 130 per minute was present. An x-ray film of the chest exhibited dense annular shadows in the left

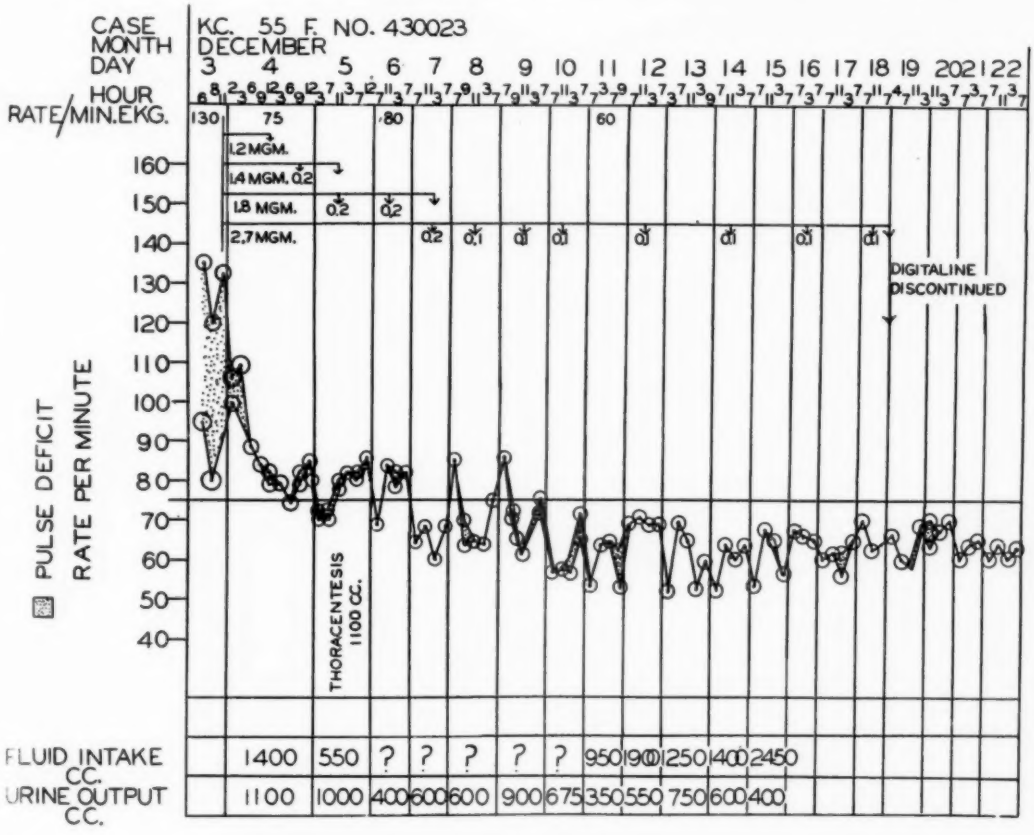
CASE KC. 55 F. NO. 430023
MONTH DECEMBER
DAY 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
HOUR
RATE/MIN. EKG.
PULSE DEFICIT
RATE PER MINUTE
1.2 MGM.
1.4 MGM.
1.8 MGM.
2.7 MGM.
THORACENTESIS 1100 CC.
DIGITALINE DISCONTINUED
FLUID INTAKE CC.
URINE OUTPUT CC.
1400 550 ? ? ? ? ? 950 1900 1250 1400 2450
1100 1000 400 600 600 900 675 350 550 750 600 400

Fig. 6.—In this figure are shown data relating to Case 7, Patient K. C. Digitoxin, 1.2 mg., was given in an initial oral dose. Subsequent oral doses are shown.

paramediastinal area and right hilum with pleural effusion at the right base. The diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, multiple pulmonary infarcts, and possibly pneumonia.

The patient was put at bed rest with fluids limited to 1,500 c.c. per day and given a 3.0 Gm. salt diet. The temperature was 102°F. on admission and ranged between 99.8 and 102° F. during the first week. Twenty thousand units of penicillin were given every three hours. One cubic centimeter of mercupurin was administered. The patient was put in an oxygen tent because of dyspnea. Digitoxin, 1.2 mg., was given in one oral dose without further delay (Fig. 6). The cardiac rate, which was 134 per minute, fell to 83 per minute twelve hours later. There were no symptoms of intoxication. Twelve hours after the initial dose 0.2 mg. were given, making a total of 1.4 mg., resulting in a fall in heart rate to 72 per minute. The rate rose again, however, and fluctuated between 72 and 86 per minute. No symptoms of overdosage occurred. A thoracentesis yielding 1,100 c.c. of serosanguinous fluid was performed to relieve the dyspnea. Digitoxin, 0.2 mg., was given daily for three days, but was reduced to 0.1 mg. because of a fall in heart rate below 70 per minute. During the last days of hospitalization, 0.1 mg. was given every other day and finally was discontinued, but auricular fibrillation persisted with a heart rate around 60.

One and two-tenths milligrams in one oral dose was not adequate to digitalize the patient, nor was 1.4 milligrams. After 0.2 mg. had been given daily for the next three days, making a total of 2.0 mg. in the four-day period, the ventricular rate remained at a satisfactory level. Since 0.1 mg. every second day was adequate maintenance in this patient, the maintenance amount over this four-day period was under 0.2 mg., making the digitalizing amount around 1.8 mg. if given in twenty-four hours (2.0 mg. less 0.2 mg.).

CASE 8 (249105) (Fig. 7, Table I).—An 85-year-old white housewife was admitted to the hospital because of dyspnea, weakness, fatigue, and swelling of the ankles of five or six days' duration.

The patient was very dyspneic and cyanotic; she appeared dehydrated. Her weight was 40.0 kilograms. Moist râles were heard at both lung bases, with pleural effusion at the right base. The heart was enlarged and auricular fibrillation with a ventricular rate of 140 per minute was present. The blood pressure was 190/100. There was moderate pitting edema of the ankles.

In view of her critical condition, the patient was digitalized immediately. Digitoxin, 1.2 mg., was given in one oral dose (Fig. 7). No further digitalis was given for the next nineteen hours, but during this time there was no appreciable fall in heart rate. Two-tenths milligram was then given by mouth. Twelve hours later the total effect of 1.4 mg. had reduced the cardiac rate to 100 per minute. No symptoms of overdosage had occurred. Three successive oral doses of 0.4 mg. of the drug were then given in an effort to bring the heart rate to 70 per minute. The following day, even though the heart rate had fallen only to 85 per minute, no digitalis was given because of nausea and vomiting. During the following three days no digitoxin was given, but the heart rate decreased to 75 per minute. A total of 2.6 mg. of digitoxin was required to reduce the heart rate to 74 per minute in 120 hours. The slow decline in the ventricular rate after the last of these doses was given indicates the continued induction of the effects of the drug after it was stopped. After four days without the drug, maintenance doses of 0.2 mg. daily were instituted, but nausea and vomiting occurred and dehydration developed. Parenteral fluids and other measures were without benefit; the heart rate increased in spite of maintenance amounts, and the patient expired on the eleventh hospital day.

It is apparent that 1.2 mg. given in one dose was inadequate, even though the patient weighed only 40.0 kilograms; that 1.4 mg. in the first twenty-four hours was insufficient, and that the addition of 1.2 mg. more, making 2.6 mg. given in two days, was the adequate amount. Nausea and vomiting occurred on the third day, indicating the slow absorption. The range between the amount

required to produce adequate slowing and that required to induce nausea and vomiting in this patient was narrow. Since a total of 2.6 mg. given in two days was adequate to slow the ventricular rate and 0.2 mg. may be taken as the maintenance amount on this second day, the digitalizing amount if given in twenty-four hours would have been around 2.4 milligrams.

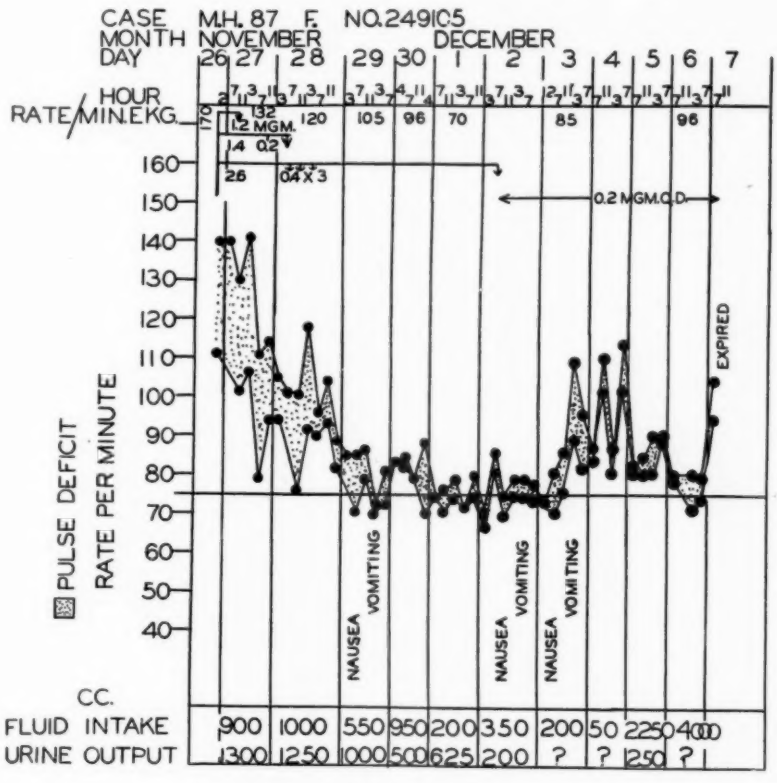

Fig. 7.—In this figure are shown data relating to Case 8, Patient M. H. Digitoxin, 1.2 mg., was given in an initial oral dose. Subsequent doses are shown.

CASE 9 (433820) (Fig. 8, Table I).—A 31-year-old white man was in good health until six weeks before admission when he suffered from sore throat with fever. He subsequently developed exertional dyspnea and noticed rapid beating of the heart. There was no previous history of rheumatic fever. Two weeks before admission he was given digitalis, but had stopped the drug several days before admission. Examination revealed a well-developed white man, weighing 58.4 kilograms, without dyspnea or cyanosis. The lungs were clear. The heart was slightly enlarged. The cardiac rhythm was auricular fibrillation; the ventricular rate was 150 per minute, and the radial, 85 per minute. There was no edema. A diagnosis of rheumatic heart disease with mitral stenosis and insufficiency was made.

The patient was kept at bed rest on a 3.0 Gm. salt diet and fluids limited to 1,500 c.c. for four days. The apical heart rate fluctuated between 100 and 140 per minute during this period. Because the ventricular rate had increased so much on the fifth hospital day, the patient was given digitoxin 1.8 mg. in one oral dose (Fig. 8). This amount induced a fall in heart rate from 140 to 70 per minute at the end of six hours. No symptoms of intoxication occurred. After twelve

hours the heart rate was still 70 per minute with a pulse deficit of 8 beats per minute. Because of beginning increase in heart rate twenty-four hours after the initial dose was given, 0.2 mg. was given. The patient was then maintained on 0.2 mg. and 0.1 mg. on alternate days, and although there were wide daily fluctuations in heart rate, the basal heart rate remained about 70 per minute.

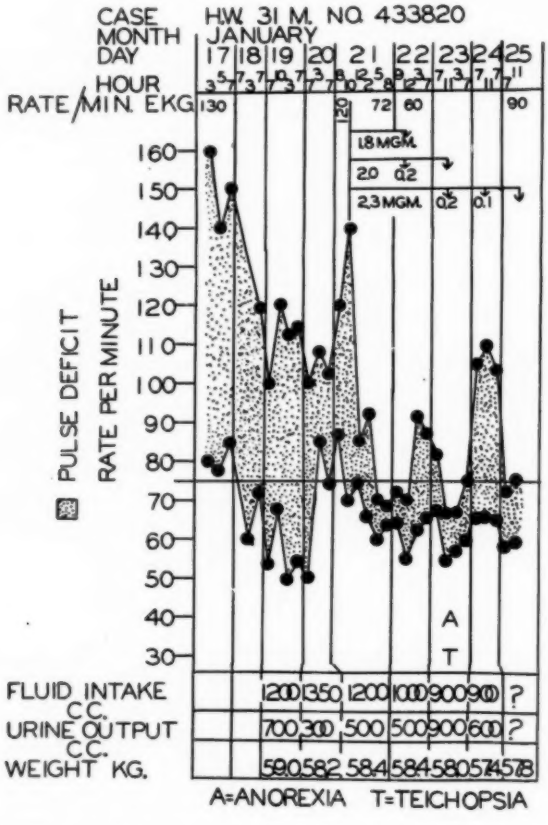

Fig. 8.—In this figure are shown data relating to Case 9, Patient H. W. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent doses are shown.

One and eight-tenths milligrams of digitoxin in one dose by mouth produced full digitalization with only slight anorexia and yellow vision.

CASE 10 (229324) (Fig. 9, Table I).—A 64-year-old white woman, with known hypertension for nineteen years, was admitted to hospital on Feb. 27, 1946, because of progressive dyspnea, orthopnea, and ankle edema of three weeks' duration following an upper respiratory infection. Three months before admission digitalis had been prescribed, but none had been taken for two months.

The patient weighed 77.0 kilograms and exhibited dyspnea and slight cyanosis. There was flatness at the right lung base, and moist râles were heard throughout both lung fields. The heart was enlarged to the left. The cardiac rhythm was auricular fibrillation; the apex rate was 130 per minute and the radial rate, 88 per minute. Ascites and moderate pitting ankle edema were present.

The patient was kept at bed rest on a 3.0 Gm. salt diet for two days. The heart rate fluctuated between 155 and 115 per minute. On the third day, digitoxin, 1.8 mg., was given in one oral

dose (Fig. 9). The heart rate fell from 136 to 120 per minute in twelve hours. In an effort to complete digitalization, 0.4 mg. was then given. The effect of a total of 2.2 mg. in twenty-four hours was to slow the cardiac rate to only 98 per minute. Moderate nausea developed at this time. A supplementary small dose of 0.2 mg. reduced the heart rate to only 95 per minute. Anorexia, without other symptoms of digitalis intoxication, persisted. A weight loss of 8.0 kilograms occurred, however, over the three-day period of digitalization, and edema nearly disappeared. The patient received 0.2 mg. daily thereafter (except on the ninth day after digitalization was started, when she received 0.4 mg.), but a cardiac rate of 80 per minute was not recorded until 3.8 mg. of digitoxin had been given over a nine-day period. On maintenance amounts of 0.2 mg. the rate continued to become slower and finally leveled around 75 per minute on the fifteenth day of therapy.

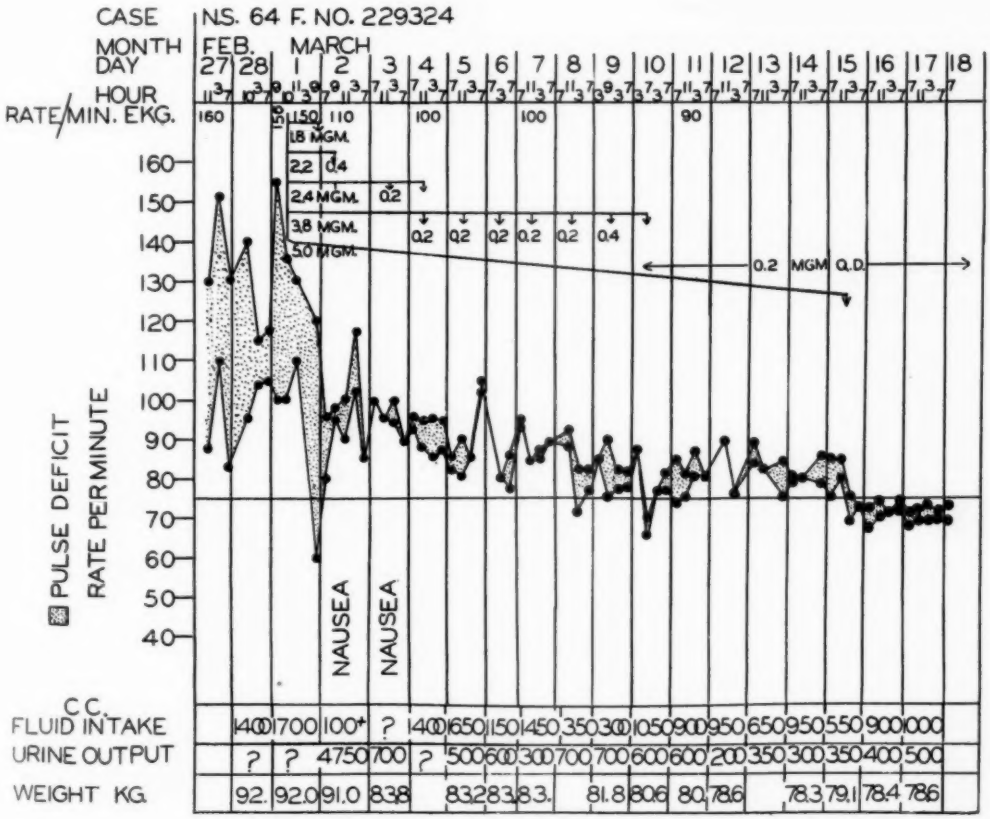

Fig. 9.—In this figure are shown data relating to Case 10, Patient N. S. Digitoxin, 1.8 mg. was given in an initial oral dose. Subsequent oral doses are shown.

It is apparent that 0.2 mg. was too much for maintenance and that the patient during this time was not adequately digitalized and was using some of the maintenance amount for digitalization. If 0.1 mg. alternating with 0.2 mg. was enough for maintenance (0.2 mg. being too much) and over the period of fifteen days the patient was given a total of 5.0 mg., 2.1 mg. of this (0.15 mg. × 14 days) was used for maintenance, leaving 2.9 mg. for digitalization if it had

been given in twenty-four hours. It is apparent from the chart that 1.8 mg., 2.2 mg., and 2.4 mg. were all inadequate, in agreement with the calculation that around 2.9 mg. was the digitalizing amount.

CASE 11 (443670) (Fig. 10, Table I).—A 70-year-old white woman was admitted to the hospital on May 3, 1946, with a history of increasing dyspnea and fatigue. During the week before admission there were several attacks of nocturnal dyspnea. The patient had been taking a liquid preparation of digitalis at times, but had received none during the two weeks before admission.

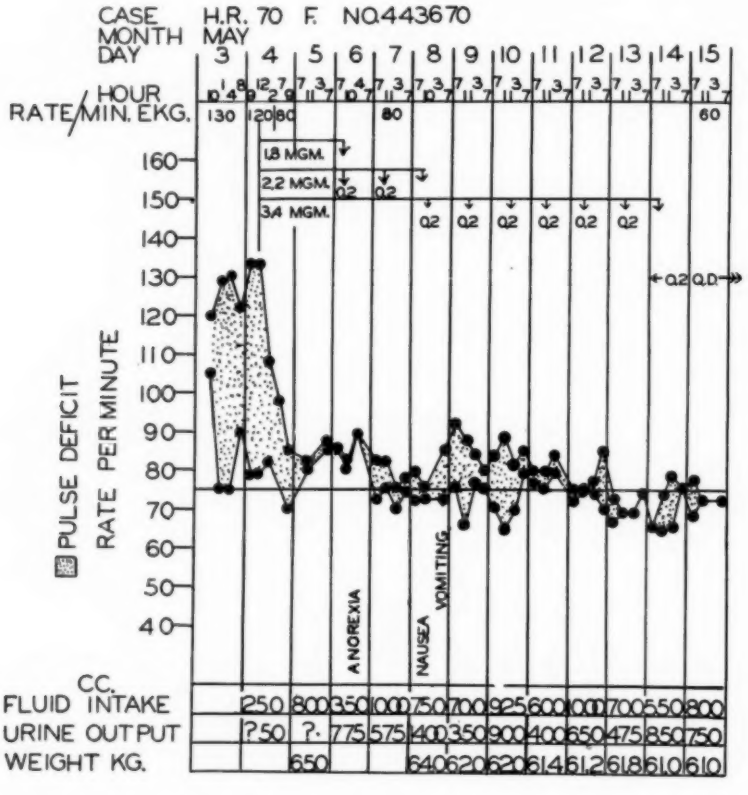

Fig. 10.—In this figure are shown data relating to Case 11, Patient H. R. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent oral doses are shown.

The patient weighed 61.0 kilograms. Many moist râles were audible in the lower one-half of both lung fields. The cardiac rhythm was auricular fibrillation, with an apical rate of 135 per minute and a radial rate of 75 per minute. No murmurs were heard. There was no edema.

The patient was observed at bed rest with a 3.0 Gm. salt diet and fluids limited to 1,400 c.c. in twenty-four hours. She received 0.5 Gm. aminophylline to relieve the dyspnea. On the following day when the cardiac rate was 134 per minute, digitoxin, 1.8 mg., was given orally in one dose (Fig. 10). After twenty-four hours the heart rate had fallen to 82 per minute. No digitalis was given for the next twenty-four hours, and forty-eight hours after the initial dose of 1.8 mg. the heart rate was 86 per minute. Two-tenths milligram was then given on two successive days, which reduced the heart rate to 76 per minute. Anorexia was observed after 1.8 mg. and nausea and vomiting occurred after 2.2 milligrams. The patient was maintained on 0.2 mg. and râles

in the chest slowly disappeared. A total of 2.2 mg. of digitoxin was required in this case to produce full digitalization.

In this patient, 1.8 mg. in one oral dose was not sufficient to slow the ventricular rate. The effect was observed for two days before additional amounts were given. The use of 0.2 mg. daily finally reduced the rate to around 75 per minute. It is likely that 0.2 mg. was slightly too much as the maintenance amount since further slowing took place with its use. It was calculated that around 2.0 mg. would have been adequate if given in twenty-four hours.

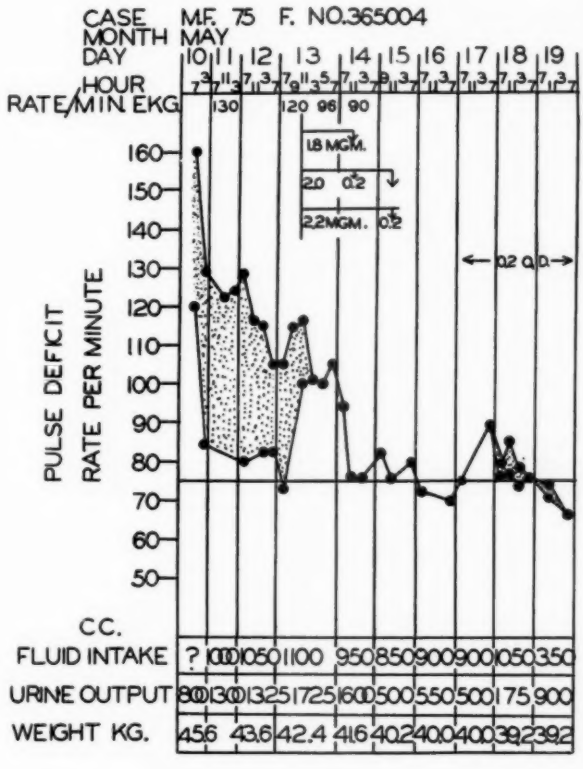

Fig. 11.—In this figure are shown data relating to Case 12, Patient M. F. Digitoxin, 1.8 mg., was given in an initial oral dose. Subsequent oral doses are shown.

CASE 12 (365004) (Fig. 11, Table I).—A 70-year-old white woman was admitted to the hospital on May 10, 1946, because of progressive dyspnea, orthopnea, and edema of the ankles of ten days' duration. The patient was known to have had hypertension for many years, but had remained free of symptoms until the present illness. The patient was dyspneic and orthopneic on admission, and the neck vessels appeared distended. She weighed 38.2 kilograms. A few moist râles were heard throughout both lungs. The cardiac rhythm was auricular fibrillation with an apical rate of 160 per minute. The heart was enlarged to the left. The liver was palpable three fingerbreadths below the costal margin. There was marked pitting edema of the ankles.

The patient was kept at bed rest and given a diet containing 3.0 Gm. of salt. The fluids were limited to 1,500 cubic centimeters. The control period was of three days' duration. During this

time she lost 3.2 kilograms in weight, the dyspnea decreased, and the heart rate fell from the admission rate of 160 per minute to range between 115 and 130 per minute, with a wide pulse deficit. On the fourth hospital day she received digitoxin, 1.8 mg., in one oral dose (Fig. 11). A fall in heart rate from 115 to 76 per minute in twenty-four hours occurred. There were no symptoms of intoxication. The dyspnea and edema disappeared without the use of other diuretics. She was given maintenance amounts of 0.2 mg. daily.

Full digitalization without symptoms of overdosage was obtained in this patient with one oral dose of 1.8 mg. of digitoxin. It is to be recalled that this patient weighed only 38.2 kilograms.

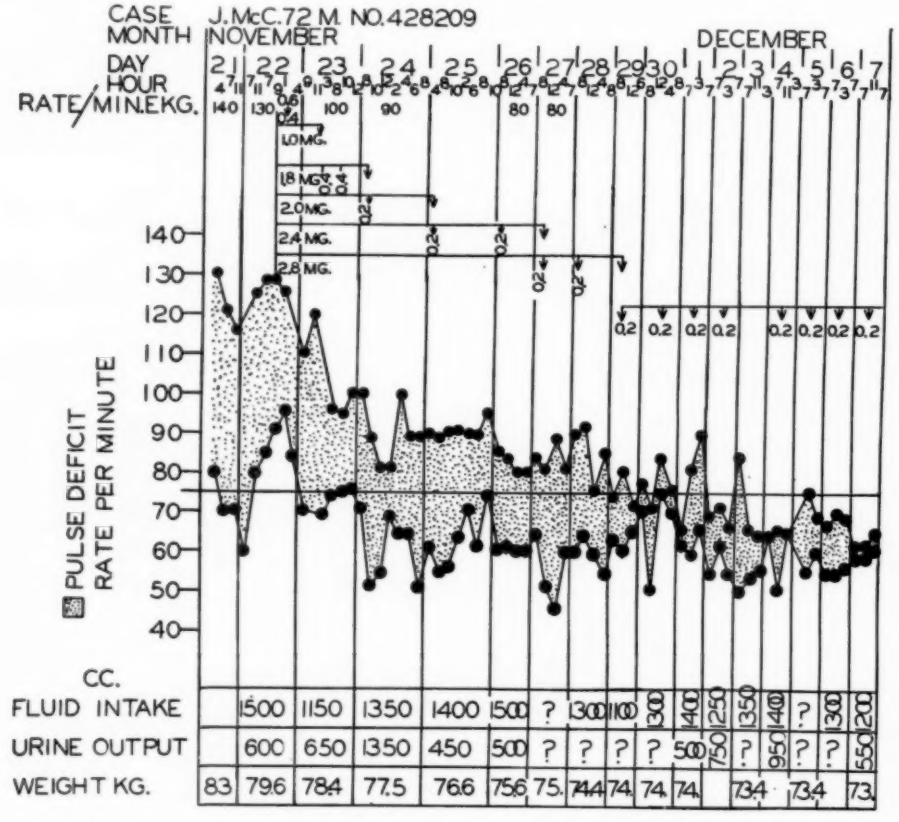

Fig. 12.—In this figure are shown data relating to Case 13, Patient J. McC. Divided doses of digitoxin were given as indicated and subsequent oral doses were given as recorded in the chart.

Case 13 (428209) (Fig. 12, Table I).—A 72-year-old white janitor was admitted to the hospital on Nov. 21, 1945, with a history of rapid heart beat, progressive dyspnea, and orthopnea of five months' duration. The patient experienced frequent attacks of precordial pain relieved by alcohol or rest. He was dyspneic, orthopneic, and cyanotic. The blood pressure was 100/70. Moist râles were heard at the bases of both lungs. The cardiac rhythm was auricular fibrillation, with an apical rate of 130 per minute and a radial rate of 70 per minute. The liver was palpable three fingerbreadths below the costal margin. There was a moderate degree of ankle edema. The diagnosis was arteriosclerotic heart disease with enlarged heart, coronary artery disease, and possible recent myocardial infarction.

The patient was given 0.5 Gm. of aminophylline and oxygen by mask to relieve the dyspnea. A 3.0 Gm. salt diet and restriction of fluids to 1,500 c.c. daily were ordered. It was planned to obtain several days of bed rest alone on this regimen to stabilize the heart rate, but because of a sudden severe attack of pulmonary edema thirty hours after admission, digitoxin 0.6 mg. was given intravenously, followed in three hours by an oral dose of 0.4 mg. (Fig. 12). After twelve hours the cardiac rate had fallen only to 120 per minute. During the second day of digitalization, 0.8 mg. additional was given, making a total of 1.8 milligrams. The following day 0.2 mg. additional was given. A total of 2.0 mg. of the drug had reduced the heart rate to only 90 per minute, but had not induced symptoms of overdosage. Subsequent small oral doses were given totaling 2.8 mg. over a six and one-half day period (Fig. 11), which represented the amount required to reduce the heart rate to 75 per minute to complete digitalization and afford maintenance. The patient was maintained on 0.2 mg. daily, except on the eleventh day after digitalization when the drug was omitted.

It is apparent that a total of 1.0 mg. orally and intravenously was insufficient to slow the rate, that the total of 1.8 mg. on the second day was inadequate, as was the total of 2.0 mg. on the third day, and so on. The rate had slowed to 75 per minute on the sixth day after a total of 2.8 milligrams. That slowing continued to occur on 0.2 mg. every day indicated that some was being used for increasing digitalization and some for maintenance, 0.2 mg. being too much for maintenance. If 0.15 mg. daily is allotted to maintenance for the five days of the six that the total of 2.8 mg. was given, we arrive at 2.1 mg. which, if given in twenty-four hours, would have digitalized this patient. That this was near the amount is indicated by the amounts which were inadequate.

Comment.—A review of the records of twenty-two hospital patients who had auricular fibrillation for which they received digitoxin disclosed that 1.2 mg. of the drug given within a twenty-four hour period generally failed to reduce the heart rate to between 70 and 75 per minute. In this analysis, the records of patients suffering from hyperthyroidism were excluded. Fourteen patients received digitoxin, 1.2 mg. (Cases 1, 2, 3, 4, 5, 6, 7, 8, 14, 15, 17, 20, 21, and 22); nine patients received the drug by mouth (Cases 5, 6, 7, 8, 14, 15, 17, 20, and 21); and five, intravenously (Cases 1, 2, 3, 4, and 22, Table I). In none of the patients who took this amount by mouth was the heart rate reduced to between 70 and 75 per minute. In one patient only was 1.2 mg. intravenously adequate (Case 1). It was noted that, in general, patients whose initial heart rates tended to be low required less digitoxin to reduce the ventricular rate to about 70 per minute. Thirteen patients, therefore, of the fifteen receiving 1.2 mg. were not adequately digitalized by this amount (Cases 2, 3, 4, 5, 6, 7, 8, 14, 15, 17, 20, 21, and 22, Table I). There was no correlation between weight of the patients and the amount of drug required to reduce the heart rate; the heart rates of the patients who weighed less were not reduced further than were the rates of the heavier patients by a given dose of digitoxin (Table I).

Four patients with auricular fibrillation were given 1.2 mg. of digitoxin in a single oral dose (Cases 5, 6, 7, 8, Table I). In none of these patients was this dose adequate for full digitalization. Supplemental oral doses were required to complete digitalization in all four patients. No evidence of digitalis intoxication occurred with 1.2 mg. of the drug.

Four patients with auricular fibrillation were given digitoxin, 1.2 mg., in a single dose intravenously (Cases 1, 2, 3, and 4). In one of these the ventricular rate was reduced to 76 per minute (Case 1); in the other three the heart rate remained above 80 per minute. Adequate digitalization was, therefore, achieved in only one of the four patients. Symptoms of intoxication occurred only once when the drug was given in this manner (Case 4). It appears, therefore, that digitalization was not obtained with 1.2 mg. in a greater proportion of patients when the drug was administered by vein than when it was given orally. It is recognized, however, that the number of cases in which this comparison is made is small.

In six patients digitalization was begun by an initial dose of 1.2 mg. and completed by supplementary doses (Cases 3, 4, 5, 6, 7, and 8). In these patients 1.2 mg. of the drug proved inadequate to digitalize, and supplementary doses were given until the heart rate fell to approximately 70 per minute. It was found that amounts totaling between 1.8 and 5.0 mg. of the drug were required to achieve digitalization in these patients in from three to fifteen days.

Four patients with rapid auricular fibrillation were given digitoxin, 1.8 mg., in a single oral dose (Cases 9, 10, 11, and 12). In two patients this amount was adequate to reduce the heart rate to 75 per minute (Cases 9 and 12). In a third patient (Case 11) 2.2 mg. of the drug were required to bring the cardiac rate below 80 per minute, and in the fourth patient (Case 10), a total of 5.0 mg. given in fifteen days was needed to complete digitalization. Symptoms of intoxication that might be ascribed to overdosage occurred in three patients (Cases 9, 10, and 11).

Ten patients with rapid auricular fibrillation received digitoxin in divided doses (Cases 13, 14, 15, 16, 17, 18, 19, 20, 21, and 22, Table I). Within the first twenty-four hours 1.2 mg. of the drug were given in several doses, but full digitalization usually was not obtained in these patients until they had been receiving the drug for several days. Corrections for daily excretions of the drug based on daily maintenance requirements allow us to arrive at an estimation of the total amount of the drug needed for digitalization if it had been given in twenty-four hours. In none of the patients was 1.2 mg. found to be adequate to reduce the heart rate to about 75 per minute. In these patients, amounts totaling from 1.8 to 3.6 mg. were required for full digitalization. The average digitalizing dose for these patients was 2.1 milligrams. Case 13 (Fig. 12, Table I) is representative of this group.

In Table I are shown the amounts of digitoxin required to achieve full digitalization in Cases 1 to 19 inclusive (excluding Case 2) with auricular fibrillation. In a number of instances digitalization was achieved only after the drug had been given for several days. In calculation of the total dose of digitoxin required in these cases, corrections for daily excretion of the drug were made. Excretion was estimated by the average amount of the drug, over a period of time, which was needed for daily maintenance after digitalization had been completed. Daily maintenance doses ranged from less than 0.1 up to 0.2 mg. daily, averaging around 0.15 mg. daily for all of the cases. The frequency curve of the amount is shown in Fig. 13,*C*. The total doses for digitalization, corrected for daily drug

excretion, appear in the appropriate column of Table I. The average corrected total dose of digitoxin required for digitalization in ten patients (Cases 3 to 12, inclusive) given 1.2 mg. and 1.8 mg. in one dose, followed by sufficient drug to achieve digitalization, was 2.06 mg., the range being 1.7 to 2.9 milligrams. If the one patient (Case 1) in whom 1.2 mg. intravenously was adequate were included, the average would be 1.98 mg., in short, 2.0 milligrams. The average for seven patients (Cases 13 to 19, inclusive) in whom the drug was given in divided doses was 2.06 mg., the range being 1.6 to 3.0 milligrams. The average for the eighteen patients was 2.01 milligrams. The amount required to digitalize when a large amount was given first, or when given in smaller amounts, turned out

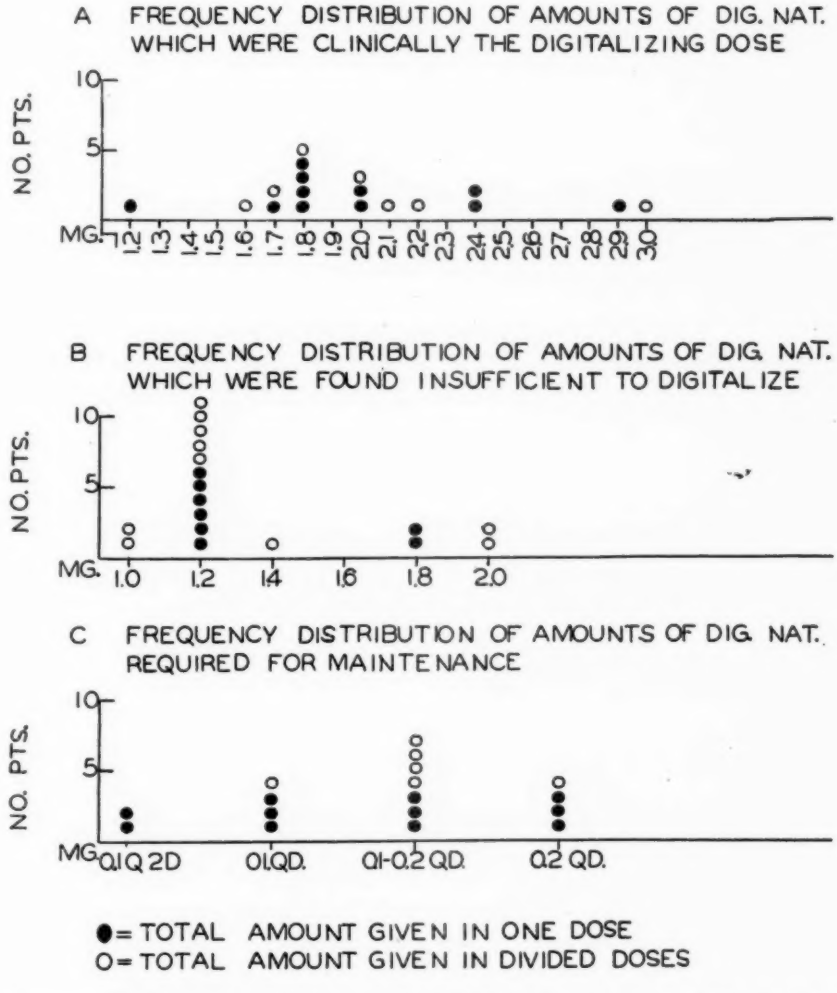
A FREQUENCY DISTRIBUTION OF AMOUNTS OF DIG. NAT. WHICH WERE CLINICALLY THE DIGITALIZING DOSE
NO. PTS.
10
5
MG.
1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7 2.8 2.9 3.0
B FREQUENCY DISTRIBUTION OF AMOUNTS OF DIG. NAT. WHICH WERE FOUND INSUFFICIENT TO DIGITALIZE
NO. PTS.
10
5
MG.
1.0 1.2 1.4 1.6 1.8 2.0
C FREQUENCY DISTRIBUTION OF AMOUNTS OF DIG. NAT. REQUIRED FOR MAINTENANCE
NO. PTS.
10
5
MG.
0.1 Q 2D
0.1 Q.D.
0.1-0.2 Q.D.
0.2 Q.D.
●= TOTAL AMOUNT GIVEN IN ONE DOSE
O= TOTAL AMOUNT GIVEN IN DIVIDED DOSES

Fig. 13.—*A*, The frequency distribution of amounts of digitoxin which were clinically the digitalizing amount in eighteen patients. *B*, The frequency distribution of amounts of digitoxin which were found insufficient to digitalize eighteen patients. *C*, The frequency distribution of amounts of digitoxin which were required for maintenance in seventeen patients.

to be approximately the same, namely, 2.0 milligrams. There was no significant difference between the amount required when part was given intravenously. The scatter diagram of the patients requiring the different amounts is shown in Fig. 13,*A* and *B*.

There were four patients in whom rapid auricular fibrillation was attributed to hyperthyroidism (Cases 23, 24, 25, and 26, Table I). It was found that larger amounts of digitoxin were required to slow the rate than in patients not suffering from this disease. Symptoms of digitalis intoxication, even after large doses of the drug had been given, did not occur. In three patients it was found impossible to slow the heart rate below 80 per minute, even when doses of 3.0 mg. or more were given in from four to eight days. In every case specific therapy for the thyrotoxicosis was withheld until observation on digitalization had been completed. The difficulty encountered in slowing the rapid heart rate of hyperthyroidism with digitoxin is similar to our experience with the whole leaf.

DISCUSSION

The subjects selected for this study were thought to form a representative cross-section of cardiac patients who need digitalis. It appears that 2.06 mg. was the average dose of digitoxin required to achieve full adequate therapeutic digitalization. In only one patient was 1.2 mg., given intravenously, sufficient. The amount that we have found necessary is in close agreement with the average amount of 2.2 mg. found by De Graff.[9]

From this experience it is apparent that digitoxin when given in adequate amounts slows the ventricular rate in auricular fibrillation as effectively as the whole leaf and brings about improvement in the patient's condition which is expected from digitalis. It is our impression, however, (1) that in order to achieve adequate slowing of the ventricular rate larger amounts are required than were expected from comparison with the experience with the whole leaf, and (2) that nausea and vomiting occur more frequently than we have been accustomed to see from the whole leaf. Whether patients can be supervised on maintenance amounts of digitoxin as easily as on the whole leaf over long periods of time is now being analyzed.

Furthermore, our observations indicate that the dose of 1.2 mg. was inadequate in most instances whether it was given intravenously or orally and whether in a single initial dose or in divided doses during the first twenty-four hours. In our experience, division of the doses in the twenty-four hours of digitalization did not increase the amount of the drug required to achieve digitalization. We digitalized certain patients in twenty-four hours by giving 1.2 or 1.8 mg. in one dose followed in each case by enough drug to achieve slowing to the desired rate. The average in these was 2.1 milligrams. In other patients the amount of the drug given in twenty-four hours by this procedure was inadequate and additional amounts had to be given for some days following. When allowance was made for maintenance over these additional days and subtracted from the total amount given the patient in that time, the amount which would have digitalized the patient if given in twenty-four hours was obtained. The average amount for the

patient digitalized in this fashion also turned out to be 2.1 mg., a very close agreement with the amount required when the drug was given over a shorter time.

Although large amounts of the drug were given in this series of patients in one single dose in order to arrive at the digitalizing amount in twenty-four hours, this procedure is not recommended for general use. It appears safe in many instances to give 1.2 mg. intravenously or orally in a single dose if it is urgent and the patient has not had digitalis in two weeks, but it is safe only because it is, in most patients, far short of the total amount eventually required for full therapeutic digitalization. If digitoxin is selected when digitalization is to be accomplished in twenty-four hours in a patient at bed rest, it may be given by mouth as follows: 0.8 mg., followed in four hours by 0.5 mg., and by 0.3 mg. four hours later still, and 0.2 mg. four hours later, and then 0.2 mg. four hours later still, if necessary; the doses after the first are not to be given if the ventricular rate slows to 75 per minute or if nausea or vomiting occurs.

The patients in this study had adequate control periods before the drug was given. It was withheld until the ventricular rate became stationary or until a rising ventricular rate indicated that the patient should not be deprived longer of the drug. The drug was given as it would be used clinically and the results are those which are encountered in clinical experience.

The maintenance amounts in our series ranged from 0.1 mg. every two days to 0.2 mg. every day, the greatest number requiring between 0.1 and 0.2 mg., namely, 0.1 alternating with 0.2 mg. on successive days. This is shown in Fig. 13,*C* which reproduces a frequency diagram of the amounts of digitoxin required in these patients for maintenance, namely, to keep the ventricular rate around 70 to 75 per minute. This is similar to De Graff's[9] experience that 0.2 mg. is too much for most patients. De Graff has pointed out that the rate of dissipation of Digitaline Nativelle is slow so that toxic symptoms may last as long as one week after its discontinuance. He warns against accumulation and overdosage by the maintenance amounts. The incidence of toxic manifestations with digitoxin when additional increments are given to slow the ventricular rate to 70 per minute and to maintain the rate around this level by rationed amounts may be accounted for by the slow rate of dissipation of the drug and the long duration of its toxic effects, as Batterman and De Graff[16] have recently pointed out.

From our studies of digitalis we have ascertained the amount required to slow the ventricular rate to from 70 to 75 per minute in patients with auricular fibrillation, and we have used this amount as that which would also be the digitalizing amount in patients with normal sinus rhythm in whom the heart rate is not a guide to digitalization. This is the best yardstick available at the present time, since patients begin to improve as digitalis is absorbed and show improvement on amounts short of the full digitalizing amount.

We believe that insistence upon 1.2 mg. as the average full therapeutic digitalizing dose of digitoxin has been unfortunate since physicians have been lulled into a false sense of security at times when they have not secured the full benefits from the use of the drug. We have seen digitalis less well administered

since this recommendation entered the literature. Moreover, acceptance of a maintenance dose of 0.2 mg. daily may be hazardous since instances of toxic effect after some months of such usage are now coming to light.

CONCLUSIONS

1. In most patients 1.2 mg. of digitoxin is insufficient to achieve adequate digitalization when given either intravenously or orally.

2. The average amount of digitoxin required for adequate digitalization in this series was around 2.0 mg. if given in twenty-four hours.

3. It makes no apparent difference in the total amount required for adequate digitalization within twenty-four hours whether the drug is given in one single dose or in divided doses.

4. When adequate slowing of the heart is attained, nausea and vomiting, in our experience, occur more frequently with digitoxin than with the whole leaf.

5. The average maintenance amount of digitoxin is between 0.1 and 0.2 mg.; 0.2 mg. is too much in most patients who have been adequately digitalized.

6. In our experience it is more difficult to keep patients in equilibrium by maintenance doses of digitoxin than with the whole leaf.

7. Although large amounts of the drug in a single dose were given in this series of patients in order to arrive at the digitalizing amount in twenty-four hours, this procedure is not recommended for general use.

8. Since the method of digitalization with divided doses of digitoxin, as recommended, is effective in patients with auricular fibrillation, the same system of dosage can be transferred to patients with normal rhythm in whom the heart rate does not serve as a guide.

9. In hyperthyroidism with auricular fibrillation, larger amounts of digitoxin are required to achieve slowing of the ventricular rate than in patients with normal basal metabolic rates, an experience which is similar to that observed when the whole leaf is used.

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CONTINUOUS OBSERVATIONS OF THE ARTERIAL OXYGEN SATURATION AT REST AND DURING EXERCISE IN CONGENITAL HEART DISEASE

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ROCHESTER, MINN.

RECENT developments in the measurement of arterial oxygen saturation in man have made continuous observations practical.[5] Application of these methods makes possible a more thorough study of the arterial oxygen saturation under a variety of conditions. It is the purpose of this paper to report on a series of continuous observations of the arterial oxygen saturation in a group of patients with congenital cardiac defects.

METHODS

The C. M. R. Model 13 compensated circuit oximeter was used in all of the observations to be reported. This instrument, described by Millikan[5] in 1942, is essentially a photoelectric colorimeter designed to measure continuously and painlessly arterial oxygen saturation in the intact human ear. The earpiece of the oximeter, which weighs approximately 30 grams, is designed to be clamped to the pinna of the ear so that it is easily possible to record arterial oxygen saturation during performance of standard exercise tests or other types of activity.

The galvanometer of the instrument can be read visually and the deflections can be recorded intermittently or the galvanometer deflections can be recorded continuously with a kymographic camera. A comparison of records made simultaneously on the same subject (Fig. 1) indicates that the intermittent observations of the arterial oxygen saturation can be made with sufficient rapidity to follow accurately the changes in saturation that may occur. We have used the intermittent type of observation (readings taken and recorded every fifteen to thirty seconds) almost exclusively because of its simplicity.

Millikan[6] reported that the range of differences between oximeter saturation readings and Van Slyke analyses of simultaneous arterial blood samples was ±5 percentage points of saturation in the saturation range from 75 to 90 per cent

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and ±8 percentage points in the saturation range from 50 to 75 per cent. The instrument was reported to indicate changes in arterial oxygen saturation with substantially greater accuracy than absolute values of saturation. Baldes and co-workers[1] in 1942, Boothby and Robinson[2] and Power and co-workers[9] in 1943, and Hemingway and Taylor[4] in 1944 obtained an accuracy similar to that reported by Millikan. One of us (G. E. M.),[7] during nearly 400 calibrations of oximeter readings against analyses (Van Slyke) of simultaneously drawn arterial blood, found that the average difference between the oximeter reading and the Van Slyke value was +4.5 percentage points in the saturation range from 50 to 91 per cent. The average deviation from Van Slyke analyses was significantly different when different earpieces were used, ranging from +2.1 to +13.1 percentage points for the six earpieces tested.

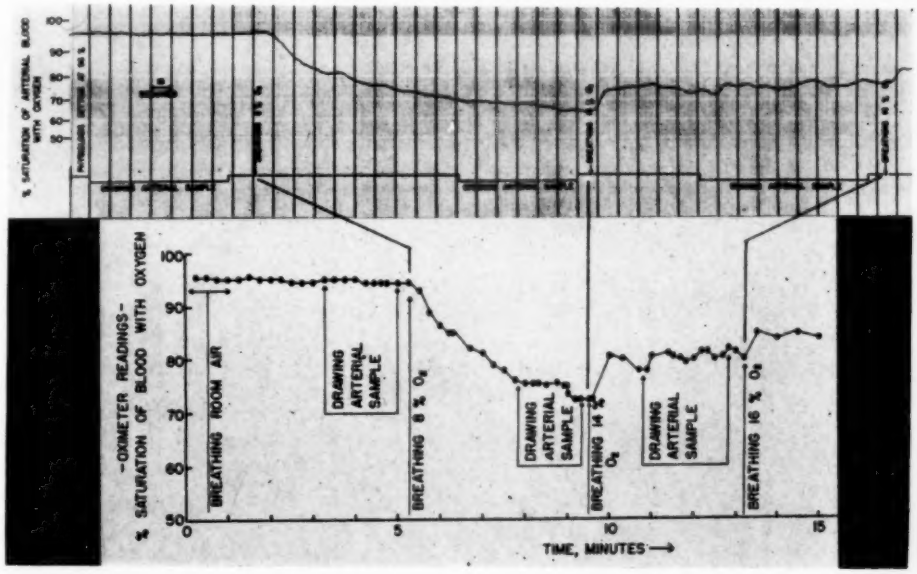

Fig. 1.—A comparison of continuous (top) and intermittent (bottom) recording of arterial oxygen saturation by means of the Millikan oximeter. These records were made simultaneously from the two ears of the same subject.

The method of collecting the data reported herein was as follows: While the patient was supine, the oximeter earpiece, already warmed up by having been turned on ten minutes earlier, was affixed to an ear. After the ear had become fully flushed (five to fifteen minutes were usually required) a clinical estimate of the patient's arterial oxygen saturation was made and the oximeter was then manually adjusted to correspond with this estimated value. Oximeter saturation readings were made and recorded every fifteen to thirty seconds from this point on. A radial arterial puncture was done under local procaine hydrochloride anesthesia shortly after the observation period was started. The oximeter reading was carefully noted at the time this sample was being drawn. In some of the tests an indwelling needle was placed in the radial artery so that

additional arterial samples could be obtained at will during the periods of exercise and recovery.

The arterial blood samples were collected under a minimal amount of mineral oil containing a small quantity of powdered heparin as an anticoagulant. A small amount of clean mercury was aspirated into the syringe, after the blood was drawn, to act as a mixing bead. The sample was tightly capped and stored in an ice bath in the dark until it was analyzed. Within an hour after the sample was drawn, analyses were carried out for oxygen content and oxygen capacity by the Van Slyke manometric method[8] as described by Roughton and co-workers.[10]

Each patient, while supine, was given 100 per cent oxygen to breathe by means of a United States Air Forces A-15 oxygen mask, the flow being controlled by means of an oxygen pressure demand regulator, United States Air Forces Type A-16. The magnitude of the increase of the oximeter saturation reading and the time required to attain the maximal value were noted. After the patient's arterial saturation had stabilized while he was breathing oxygen, the gas was then administered under a positive pressure of from two to four inches (5 to 10 cm.) of water (by means of the A-16 regulator) and the effect on the oximeter saturation reading was noted. The patient was then allowed to breathe room air again and the time required for the oximeter saturation reading to return to the original value was recorded. Next the patient stood up and remained standing quietly at the bedside until the saturation level became stable. He then began walking on a treadmill at 1.7 miles per hour. The patient was exercised on the treadmill for a maximum of five minutes. The exercise test was terminated earlier if the patient developed severe respiratory or circulatory distress. The patient reclined immediately after the exercise test and was observed until he had regained the original resting saturation value.

After all of the oximeter observations on the patient had been completed, each oximeter reading was corrected by addition, or subtraction, of the amount of the difference that was present between the initial resting per cent saturation value determined by Van Slyke analysis of the arterial blood and the average actual oximeter saturation reading during the period that the arterial sample was being drawn. The magnitude of the theoretical error resulting from the thus unavoidably introduced error in the initial adjustment of the oximeter saturation reading has been calculated.* The difference between the decrease in arterial

*Equation for calculation of the theoretical change in arterial saturation from the change in arterial saturation indicated by the oximeter when the initial adjustment of the saturation reading of the instrument has been incorrectly made is $S_x = \frac{(BT_1 + S_0)\ (BT_2 + S_2)}{(BT_1 + S_1)} - (BT_2)$, in which B represents bias ratio setting of oximeter; T_1, initial ear thickness reading in millimeters†; T_2, final ear thickness reading in millimeters†; S_0, correct initial saturation reading in millimeters† (from Van Slyke analysis of arterial blood); S_1, initial saturation reading in millimeters (as instrumentally adjusted by operator); S_2, final saturation reading in millimeters†; and S_x,‡ final saturation reading in millimeters† if initial instrumental adjustment had been correct.

†Galvanometer deflection in millimeters above 50 per cent saturation on the galvanometer scale.

‡Millimeter "saturation readings" can be converted to percentage saturation by the following equation: $P = 100\ \left(1 - e^{-\frac{S}{1.444K}}\right) + 50$, in which S represents the saturation reading in millimeters†; K, the number of millimeters between 50 per cent and 100 per cent saturation on the oximeter scale; and e equals 2.718.

These equations were derived by R. E. Jones, B.E.E., Consulting Engineer, Mayo Clinic.

oxygen saturation produced by exercise as read on the oximeter and the theoretical decrease in saturation which would have been indicated by the oximeter if the initial setting had been correct ranged from −2 to +3 percentage points, the average being +0.7 per cent saturation (Table I). It is of practical interest that the magnitude of the theoretical errors in oximeter readings when the instrument is used in this manner is less than the inherent error which has been reported for the instrument.

TABLE I. THE CALCULATED THEORETICAL ERRORS IN THE CHANGES IN ARTERIAL SATURATION INDICATED BY THE OXIMETER WHICH RESULT FROM THE DISPLACEMENT OF THE OXIMETER SCALE AND WHICH ARE INTRODUCED WHEN THE INSTRUMENT IS INITIALLY ADJUSTED TO INDICATE A SATURATION VALUE BASED ON A CLINICAL ESTIMATE OF THE DEGREE OF CYANOSIS

PATIENT	INSTRUMENTAL SETTING OF OXIMETER AT REST (%)*	ARTERIAL SATURATION AT REST, VAN SLYKE ANALYSIS (%)*	OXIMETER READING DURING EXERCISE (%)*	INDICATED DECREASE IN ARTERIAL O_2 SATURATION (OXIMETER) (%)*	CALCULATED INDICATED DECREASE IN ARTERIAL O_2 SATURATION IF OXIMETER HAD BEEN CORRECTLY SET AT REST† (%)*	THEORETICAL ERROR IN OXIMETER READING DUE TO INCORRECT INSTRUMENTAL SETTING (%)*
				"A"	"B"	"B" − "A"
1	83	87	71.0	12.0	11.0	+1
2	77	79	61.5	15.5	15.5	0
3	73	53	52.0	21.0	18.0	+3
4	75	45	64.0	11.0	8.0	+3
5	91	81	85.5	5.5	5.5	0
6	90	79	83.0	7.0	6.5	+0.5
8	73	79	45.0	28.0	29.5	−1.5
9	75	91	66.5	8.5	10.5	−2.0
10	74	67	56.0	18.0	16.0	+2.0
11	80	79	68.0	12.0	11.5	+0.5
12	73	67	62.0	11.0	10.5	+0.5
14	80	68	73.5	6.5	5.5	+1.0
15	73	71	59.0	14.0	13.5	+0.5
Mean	78.2	72.8	65.2	13.1	12.4	+0.7

*Per cent arterial oxygen saturation.
†Data calculated from the equation given in the footnote on p. 670.

RESULTS

The data presented in this paper were obtained during studies conducted on twenty patients seen at the Mayo Clinic between September, 1946, and May, 1947. Fifteen of these patients had a cyanotic type of congenital cardiac defect. The fifteen cases included the tetralogy of Fallot, Eisenmenger complex, and interventricular and interatrial septal defects with right to left shunts. The ages of these fifteen patients ranged from 3½ to 30 years. Nineteen students, technicians, and doctors, whose ages ranged from 9 to 60 years, were used as

normal controls in this study. The results obtained from these two groups are presented in Table II.

The responses of the arterial oxygen saturation of the group of normal subjects to the various conditions imposed on them were remarkably uniform. There was no significant difference in the responses of the two sexes or of different age groups. When the normal individuals under ordinary resting conditions were given pure oxygen to breathe, their oximeter saturation readings increased from 1 to 5 percentage points (mean increase, 2.7 percentage points), substantiating Boothby and Robinson's findings. These results indicate that the arterial oxygen saturation of normal subjects ranges from 95 to 99 per cent (mean, 97.3 per cent) at the altitude of 1,000 feet where these measurements were made. This normal group attained oximeter saturation readings of 100 per cent in from 0.5 to 3.0 minutes (mean, 1.3 minutes) after they started breathing pure oxygen. These times are slightly longer than those reported by Fowler and Comroe.[3] Giving the oxygen under positive pressure up to four inches (10 cm.) of water caused no further increase in their arterial oxygen saturation. When individuals of the normal group stood upright (from a supine position) and when they walked on the treadmill for five minutes at 1.7 miles per hour, there was no significant change in their arterial oxygen saturation.

The average resting arterial oxygen saturation of the cyanotic patients was 71 per cent (range, 45 to 91 per cent), while in normal subjects, the saturation was found to be 98 per cent. The mean erythrocyte count of the cyanotic individuals was 6,480,000 per cubic millimeter and their hematocrit values averaged 70 per cent (Table III). This group of patients gave responses widely different from those of the normal individuals. Breathing pure oxygen produced an increase in oximeter saturation reading of from 2.0 to 16.5 percentage points (mean, 6.2 percentage points). The time required to attain the maximal saturation reading when 100 per cent oxygen was breathed ranged from 1.0 to 6.0 minutes (mean, 3.0 minutes). When pure oxygen was administered to these cyanotic patients, under positive pressure, oximeter saturation readings increased, on the average, 1.6 percentage points over the saturation values attained with pure oxygen administered with no positive pressure.

The individuals in the cyanotic group had changes in oximeter saturation readings ranging from +3.0 to −10.0 percentage points (mean, −2.4 percentage points) when they went from the supine to the erect position. In the cyanotic patients, walking on the treadmill at 1.7 miles per hour produced decreases in oximeter saturation readings of from −3.5 to −19.0 percentage points (mean, −10.9 percentage points). The exercise was terminated in less than 5.0 minutes in six instances because the patients were in distress or were fatigued. Four of the patients were unable to exercise longer than three minutes. Average duration of the exercise was 4.2 minutes.

Five patients who had noncyanotic types of congenital cardiac defects were studied (Table IV). Their ages ranged from 2½ to 19 years. Their lesions included atrial and ventricular septal defects and one patent ductus arteriosus. The values for the arterial oxygen saturations of these individuals obtained in

TABLE II. THE RESPONSE OF THE ARTERIAL OXYGEN SATURATION (OXIMETER READING) OF PATIENTS WITH A CYANOTIC TYPE OF CONGENITAL CARDIAC DEFECT TO VARIOUS CONDITIONS*

PATIENT		INCREASE IN OXIMETER SATURATION READING WITH 100% O_2 (%)†	TIME TO REACH MAXIMAL INCREASE (MIN.)	EFFECT OF PRESSURE‡ BREATHING WITH O_2 (%)†	TIME TO RETURN TO CONTROL VALUE (MIN.)	EFFECT OF STANDING POSTURE (%)†	DURATION OF WALK AT 1.7 M.P.H. (MIN.)	EFFECT OF WALK (%)†	TIME FROM START OF WALK TO MAXIMAL SATURATION CHANGE (MIN.)	TIME FROM END OF WALK TO CONTROL VALUE (MIN.)
1		5.5	1.0	——	2.0	−2.0	4.5	−17.0	4.5	4.0
2		7.0	2.5	+2.5	——	−3.5	5.0	−12.0	5.0	6.0
3		——	——	——	——	−5.0	1.5	−9.0	2.5	3.0
4		2.0	0.5	+3.0	2.0	+3.0	5.0	−14.0	5.0	5.5
5		16.5	4.0	0.0	4.5	0.0	5.0	−6.0	1.0	——
6		5.5	4.0	——	3.0	−6.0	3.0	−4.0	3.0	1.0
7		4.0	6.0	——	2.5	——	——	——	——	——
8		5.5	1.75	——	3.75	−10.0	5.0	−18.5	5.5	4.0
9		6.5	4.0	0.0	3.5	−1.5	5.0	−3.5	3.5	2.0
10		6.0	4.0	+5.0	1.5	−3.0	4.75	−14.0	4.75	3.0
11		6.5	3.0	+1.0	4.0	0.0	5.0	−8.5	2.5	2.5
12		3.0	1.5	——	1.5	−6.0	2.75	−6.0	2.75	2.5
13		5.0	2.0	0.0	1.0	+2.0	5.0	−13.5	3.0	7.0
14		7.0	4.0	——	2.2	−2.0	5.0	−8.0	3.2	3.0
15		6.0	3.0	——	2.0	0.0	2.75	−19.0	2.75	3.75
Mean of patients' values		6.2	3.0	+1.6	2.6	−2.4	4.2	−10.9	3.5	3.6
Values for 19 normal subjects	Mean	2.7	1.3	+0.1	2.8	0.0	5.0	−0.3	——	——
	Range	+1.0 to +5.0	+0.5 to +3.0	0.0 to +1.0	+1.0 to +5.0	−1.0 to 0	——	−2.0 to 0	——	——

*Average values obtained from normal individuals under similar conditions are given in the last line.
†Percentage points of arterial oxygen saturation.
‡A positive pressure of 2 to 4 inches (5 to 10 cm.) of water was used.

TABLE III. RESULTS OF ANALYSES OF ARTERIAL BLOOD FROM PATIENTS WITH CYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS*

PATIENT	SEX	AGE (YR.)	DIAGNOSIS	ARTERIAL O_2 CONTENT (VOL. %)	ARTERIAL O_2 CAPACITY (VOL. %)	ARTERIAL O_2 SATURATION (%)	HEMOGLOBIN† (GM. PER 100 C.C.)	ERYTHROCYTES (MILLIONS)	HEMATOCRIT (%)
1	F	5	Tetralogy	17.0	19.5	87	14.6	4.30	—
2	F	15	Indeterminate; ? tricuspid atresia	20.1	25.3	79	18.9	6.11	65
3	M	3.5	Tetralogy	13.9	26.2	53	19.6	5.34	65
4	F	13	Tetralogy and dextrocardia	15.1	33.6	45	25.1	7.31	80
5	F	16	Atrial septal defect	17.9	22.2	81	16.6	——	50
6	M	16	Cor triloculare and dextrocardia	18.3	23.2	79	17.3	4.51	55
7	M	7	Tetralogy	18.4	29.0	63	21.6	8.27	89
8	M	5	Tetralogy	25.5	32.4	79	24.2	8.02	84
9	M	30	Eisenmenger complex	22.5	24.7	91	18.4	5.32	60
10	F	8	Tetralogy	21.7	32.2	67	24.0	7.95	80
11	F	14	Atypical tetralogy	17.7	22.3	79	16.6	4.12	52
12	M	4	Tetralogy	18.7	28.1	67	21.0	8.13	86
13	M	16	Tetralogy	——	——	—	——	6.45	63
14	M	8	Tetralogy	22.5	33.2	68	24.8	7.54	78
15	F	7.5	Tetralogy	20.9	29.4	71	21.9	7.41	74
Mean values for patients				19.3	27.2	71	20.3	6.48	70
Mean values for 19 normal subjects				19.7	20.1	98	15.0	4.75‡	50‡

*Mean values for normal subjects are included in the last line of the table.

†Hemoglobin concentration was calculated from the oxygen capacity of the blood (volumes per cent capacity ÷ 1.34 = grams of hemoglobin per 100 c.c. of blood).

‡Analyses of venous blood samples were made by the hematology laboratories of the Mayo Clinic.

TABLE IV. RESULTS OF ANALYSES OF ARTERIAL BLOOD FROM PATIENTS WITH NONCYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS

PATIENT	SEX	AGE (YR.)	DIAGNOSIS	ARTERIAL OXYGEN CONTENT (VOL. %)	ARTERIAL OXYGEN CAPACITY (VOL. %)	ARTERIAL OXYGEN SATURATION (%)	HEMOGLOBIN, GM. PER 100 C.C. (CALCULATED FROM O_2 CAPACITY)	ERYTHROCYTES (MILLIONS)
16	M	16	Interatrial septal defect	19.1	19.5	98	14.6	——
17	F	5	Interventricular septal defect	14.9	15.4	97	11.5	4.27
18	F	19	Atrial and ventricular septal defects	15.7	16.7	94	12.5	——
19	F	2.5	Patent ductus arteriosus	15.1	16.7	90	12.5	4.69
20	F	5	Interauricular septal defect	17.9	19.4	92	14.5	4.68
Mean		9.5		16.5	17.5	94	13.1	4.55

TABLE V. THE RESPONSES OF THE ARTERIAL OXYGEN SATURATION (OXIMETER READING) OF PATIENTS WITH NONCYANOTIC TYPES OF CONGENITAL CARDIAC DEFECTS TO VARIOUS CONDITIONS

PATIENT	INCREASE IN OXIMETER SATURATION READING WITH 100% O_2 (%)*	TIME TO REACH MAXIMAL INCREASE (MIN.)	EFFECT OF PRESSURE† BREATHING WITH O_2 (%)*	TIME TO RETURN TO CONTROL VALUE (MIN.)	EFFECT OF STANDING POSTURE (%)*	DURATION OF WALK AT 1.7 M.P.H. (MIN.)	EFFECT OF WALK (%)*	TIME FROM START OF WALK TO MAXIMAL SATURATION CHANGE (MIN.)	TIME FROM END OF WALK TO CONTROL VALUE (MIN.)
16	4.0	1.0	0.0	1.5	0.0	5.0	−2.0	0.5	0.5
17	——	——	——	——	0.0	5.0	0.0	——	——
18	3.0	3.0	0.0	3.0	−4.0	5.0	−1.0	1.5	2.5
19	——	——	——	——	+2.0	3.0	−3.5	3.0	——
20	5.0	1.0	+0.5	2.0	0.0	5.0	−3.0	1.0	2.0
Mean	4.0	1.7	+0.2	2.2	−0.4	4.6	−1.9	1.5	1.7

*Percentage points of arterial oxygen saturation.
†A positive pressure of 2 to 4 inches (5 to 10 cm.) of water was used.

TABLE VI. COMPARISON OF OXIMETER SATURATION READINGS WITH ARTERIAL OXYGEN SATURATION VALUES DETERMINED BY VAN SLYKE ANALYSES OF SIMULTANEOUSLY DRAWN ARTERIAL BLOOD AT REST AND DURING EXERCISE

PATIENT	HEMOGLOBIN (GM. PER 100 C.C.)	OXIMETER READING AT REST (%)*	OXIMETER READING DURING EXERCISE (%)*	OXIMETER CHANGE DURING EXERCISE (%)*	ARTERIAL SATURATION AT REST (VAN SLYKE) (%)*	ARTERIAL SATURATION DURING EXERCISE (VAN SLYKE) (%)*	SATURATION CHANGE DURING EXERCISE (VAN SLYKE) (%)*	DIFFERENCE IN RECORDED CHANGE (VAN SLYKE AND OXIMETER) (%)*
21	25.2	67	57	−10	86	69	−17	− 7
22	26.2	53	46	− 7	58	44	−14	− 7
23	11.9	90	70	−20	86	53	−33	−13
24	12.2	90	89	− 1	96	98	+ 2	+ 3
25	25.4	63	48	−15	81	45	−36	−21
Mean	20.2	72.6	62	−10.6	81.4	61.8	−19.6	− 9.0

*Percentage saturation of blood with oxygen.

response to the various tests (Table V) lay between those obtained from the normal group and those obtained from the cyanotic group.

Inasmuch as the scale of the oximeter is calibrated to read only from 50 to 100 per cent saturation, and since some cyanotic patients have resting arterial oxygen saturations of less than 50 per cent, a further effort was made to determine if the instrument gives reliable measurements of the saturation changes occurring in these very low ranges. Arterial blood samples were taken before and during exercise on five patients, four of whom had arterial oxygen saturation values that were markedly changed by exercise. The arterial oxygen saturation as determined by Van Slyke analyses of these blood samples has been compared with simultaneous oximeter readings (Table VI). In these instances, the change in arterial saturation during exercise, as indicated by the oximeter, differed by +3 to −21 percentage points from the change in arterial saturation found by Van Slyke analyses of the arterial blood. The average difference was −9.0 percentage points.

COMMENT

The use of the oximeter in studying patients with congenital heart disease offers several advantages. Continuous observation of the arterial oxygen saturation is possible. True values of the resting arterial oxygen saturation can thus be estimated if one waits until the patient is resting comfortably before making the instrumental saturation reading and then notes carefully the changes in saturation which may occur during the period of the arterial puncture. Fig. 2 gives an example of the marked decrease in the oximeter saturation reading which may occur in an infant as a result of crying and struggling when an arterial puncture is done. A patient's response to standardized procedures, such as exercising or breathing 100 per cent oxygen, may be studied continuously with ease. Pre- and postoperative studies made with an oximeter (Figs. 3 and 4) may be of much more significance and may give more information than a single arterial oxygen analysis done before and after surgical intervention.

The chief disadvantage of the oximeter in studies on cyanotic patients is the large range of error inherent in the instrument in the lower ranges of arterial saturation. The relatively large discrepancies found between oximeter readings during exercise and analysis of simultaneous arterial samples obtained in four cyanotic, polycythemic patients may indicate that the range of error is greater in patients of this type than it is in normal subjects rendered anoxic by exposure to high altitude or to low-oxygen, high-nitrogen mixtures.

Since the oximeter measures only *changes* in the arterial oxygen saturation, it is necessary to make a "setting" of the instrument at some value before observations are started. When it is used on normal subjects, an initial "physiologic setting" of the instrument to read 98 per cent saturation (subject breathing room air) is made and all subsequent saturation changes are measured from this point. However, when one is using the oximeter on individuals whose arterial oxygen saturation may not be normal, one is no longer justified in making such an arbitrary "physiologic setting" of the instrument but must do an arterial puncture and Van Slyke analysis for oxygen at some time during the course of the observa-

tions to establish a reference point for all of the readings made before and after the arterial puncture. This correction of the oximeter readings is somewhat inconvenient but is necessary to relate instrumental readings to actual arterial saturation values. It is of practical convenience that, theoretically, the oximeter records changes in arterial saturation with only relatively small errors in spite of considerable displacement of the saturation scale which may result when initial instrumental settings are made without a knowledge of the actual arterial saturation level, as is often the case when one is dealing with cyanotic patients. However, it should be kept in mind that even at best the range of error in oximeter readings is relatively large. This range of error may be even greater when one is dealing with patients with varying degrees of polycythemia, abnormal skin pigmentation, and so forth (Table VI).

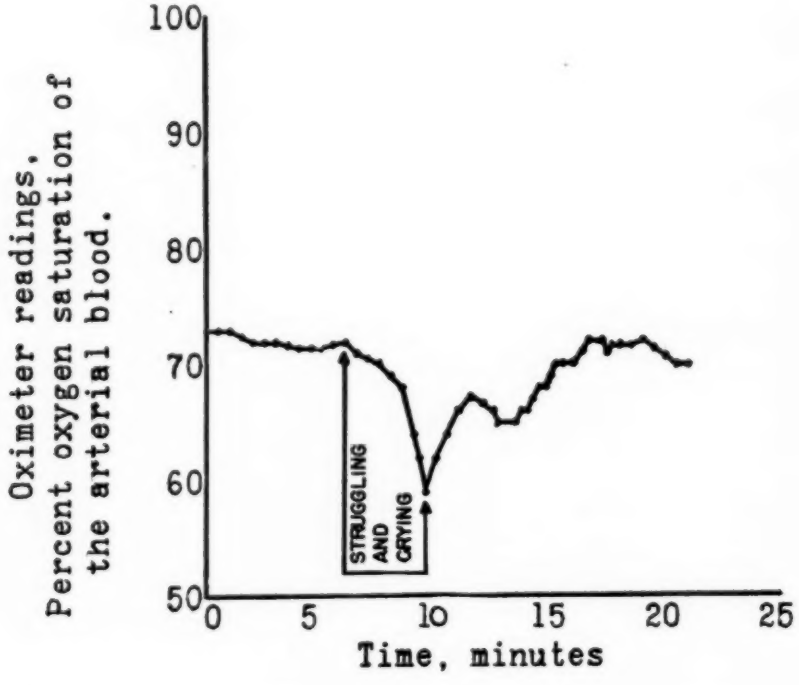

Fig. 2.—The effect of the crying and struggling associated with an arterial puncture on the arterial oxygen saturation. The patient was 13 years old. The diagnosis was cyanotic congenital heart disease.

An occasional shortcoming of the oximeter occurs when a patient is encountered whose ears are too small to accommodate the present earpieces. This condition occurs frequently in infants and women and prohibits oximeter studies on these individuals. Also, some Negroes and others with a very heavily pigmented

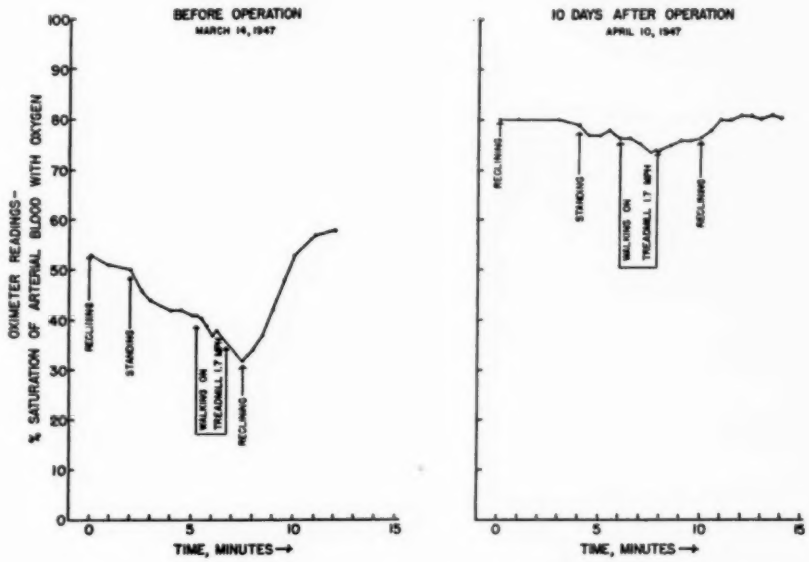

Fig. 3.—The effect of the Blalock operation on the arterial oxygen saturation at rest and during exercise in Patient 3, 3½ years of age. The diagnosis was the tetralogy of Fallot. Ten days after the operation the resting arterial oxygen saturation was increased 28 percentage points, and the magnitude of the decrease of the arterial oxygen saturation produced by exercise was reduced from 20 to 7 percentage points.

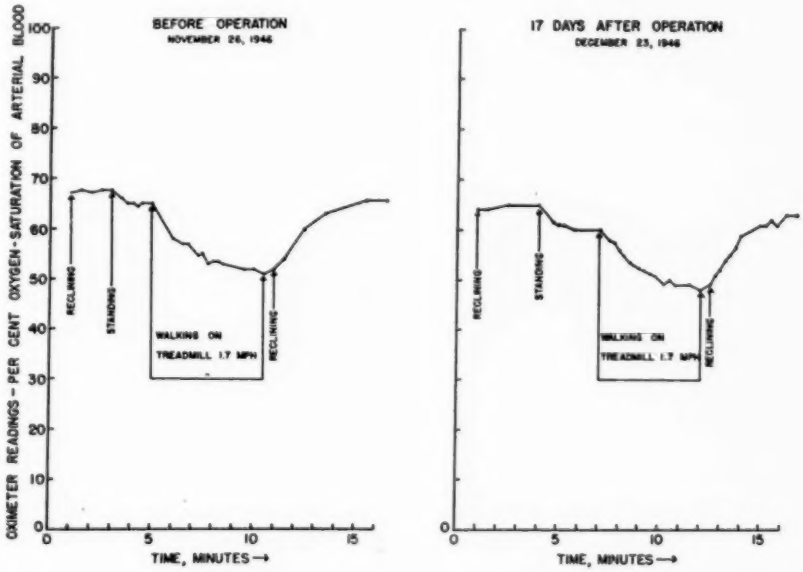

Fig. 4.—A comparison of the arterial oxygen saturation at rest and during exercise before and after a Blalock type operation in which the anastomosis was not satisfactory. This result was secured in Patient 10, 8 years of age. The diagnosis was the tetralogy of Fallot. The resting arterial oxygen saturation and the response to exercise were not significantly altered by the operation.

skin may not be suitable for oximetric measurements because of the spectral transmission characteristics of their ears. It has been found that there is a relatively greater absorption of the light in the spectral region from 600 to 800 millimicrons by the colored ear than by the normal white ear. This particular spectral region activates the "red cell" of the oximeter earpiece; hence, variations in this region may critically alter the function of the oximeter. Except for the two groups of patients just mentioned, however, the oximeter finds nearly universal applicability for continuous indication of variations in arterial oxygen saturation.

The most clear-cut and significant differences in the responses of the arterial oxygen saturation of the normal subjects and of the cyanotic group of patients were seen when the positions of the patients were changed or when exercising was done. The subjects in the normal group caused practically no change in oximeter saturation readings when they stood up (from a supine position) or when they exercised by walking on a treadmill for five minutes at 1.7 miles per hour. The individuals of the cyanotic group, however, characteristically caused a decrease (mean, 2.4 percentage points) in oximeter saturation readings when they stood upright and more severe decreases (mean, 10.9 percentage points) when they walked at 1.7 miles per hour for an average of 3.5 minutes. A walking-exercise test was chosen because it was familiar to everyone and required no training for its performance. Furthermore, it called into action the most commonly used large muscle groups of the body. Even the 3-year-old patients were able to co-operate by walking on the treadmill as desired.

The decrease in the arterial oxygen saturations of the cyanotic individuals during exercise was an indication of the inability of the heart to pump enough blood through the lungs to keep the oxygen replaced that was being lost at an accelerated rate in the muscle tissue. Thus, these responses would seem to be an index to the severity of the right to left intracardiac shunt and the proportion of blood that enters the pulmonary circulation.

In the group of patients with cyanotic heart disease it was possible to demonstrate a significant inverse correlation (correlation coefficient, -0.6) between the resting arterial oxygen saturation and the hemoglobin content of the blood. Likewise, there tended to be a correlation (correlation coefficient, $+0.4$) between blood hemoglobin content and the decrease in oximeter saturation reading that occurred during the exercise test (Tables II and III). These relationships are readily understood since the degree of hypoxia is one of the factors which regulate the erythrocyte and, hence, the hemoglobin content of the circulating blood.

It is of interest to note that the magnitude of the increase and the time required for these cyanotic patients to attain maximal arterial oxygen saturation when breathing pure oxygen exceeded the values obtained from normal subjects. These findings are apparently the result of the continuous mixing, in the left side of the heart, of the blood from the lungs (completely saturated and carrying approximately 2 volumes per cent of oxygen in physical solution) with mixed venous blood from the right side of the heart passing through the septal defect. Under these conditions the maximal arterial oxygen saturation increase possible and the time required to attain this maximum depend on the proportion of the

venous blood going through the lungs and passing through the shunt and on the circulation time. If the arteriovenous difference remains constant, maximal saturation of the peripheral arterial blood is approached asymptotically as successive circulations of the blood increase (but by ever-lessening amounts) the oxygen saturation of the venous blood reaching the right side of the heart.

SUMMARY

Continuous observations, made with the Millikan compensated circuit oximeter, of the arterial oxygen saturation of nineteen normal subjects and of twenty patients with cyanotic and noncyanotic types of congenital cardiac defects are presented.

When normal individuals were given pure oxygen to breathe, their arterial oxygen saturation increased, on the average, 2.7 percentage points (to reach 100 per cent saturation) in 1.3 minutes. In fifteen patients with a cyanotic type of congenital cardiac defect, breathing pure oxygen produced an average increase in oximeter saturation reading of 6.2 percentage points attained in an average period of 3.0 minutes.

Normal subjects showed practically no change in their arterial oxygen saturation when they changed from the supine to the erect position or when they walked on a treadmill for five minutes at 1.7 miles per hour. Patients with a cyanotic type of congenital cardiac defect showed an average decrease in oximeter saturation reading of 2.4 percentage points when they stood up and 10.9 percentage points when they exercised on the treadmill.

It is suggested that the compensated circuit oximeter is of considerable value in studying patients with congenital cardiac defects for two reasons: (1) Its use in conjunction with Van Slyke analyses of arterial blood makes possible a more accurate estimation of the resting arterial oxygen saturation of such patients. (2) Measurements of the arterial oxygen saturation can be made continuously during the performance of various cardiovascular and respiratory function tests, thus greatly facilitating an objective interpretation of the results obtained. Such tests serve as a valuable adjunct in the judging of the efficacy of corrective surgical procedures in these patients.

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CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

Report of Eight Hundred Sixty-six Cases, Four Hundred Fifty With Necropsy Examination*

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(*Continued from page 526*)

PATHOLOGIC DATA

The protocols of the 450 patients who died varied greatly in detail and accuracy, since the necropsies were performed all over the world and by many different individuals. The hearts from only twenty were available to the Army Institute of Pathology, but blocks of tissue, paraffin blocks, and slides were contributed in practically all cases, and these were carefully studied, additional sections being made and special stains being used when desirable. Tissues of sections of the myocardium and of one or more of the larger coronary arteries were available in most cases.

Size of the Hearts.—The weights of 374 of the hearts were recorded. Since no comment was made regarding the size of the other seventy-six hearts, it may safely be assumed that practically all of them appeared to the prosectors to be of normal size. In arriving at the degree of hypertrophy of the hearts, the tables of normal weights of hearts correlated with body weight, as prepared by H. L. Smith[142] in 1928, were used as the starting point. Then the following heart weights were arbitrarily devised.

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DEGREE OF HYPERTROPHY OF HEARTS

GRADE	GRAMS IN EXCESS OF AVERAGE
0	49
0+	50 to 74
1	75 to 112
1+	113 to 149
2	150 to 187
2+	188 to 224
3	225 to 262
3+	263 to 299
4	300 to 375
4+	Over 376

Thus, if a heart weighed 573 grams instead of the 323 grams which would be normal according to Smith's table, hypertrophy would be considered to be Grade 3 on the basis of these criteria.

Table XXVIII shows the degree of hypertrophy observed in the 450 cases. According to this listing, 232 (52 per cent) of the hearts of those patients were hypertrophied to some extent, and seventy (16 per cent) were hypertrophic, from Grade 2 to Grade 4+. Inasmuch as there were very few cases of hypertension in the whole series (not more than fifteen or sixteen patients were known to have hypertension at the time of death, eight of whom were only slightly hypertensive, and only six of whom had valvular disease that might have caused hypertrophy), these figures are arresting. In 205 cases roentgenograms of the chest at induction showed the cardiac shadows of all patients to be within normal limits.

TABLE XXVIII. CARDIAC HYPERTROPHY IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

GRADE OF HYPERTROPHY*	NO.	%
None or probably none†	218	48.4
0+	40	8.9
1	78	17.3
1+	44	9.8
2	30	6.7
2+	11	2.4
3	9	2.0
3+	8	1.8
4	9	2.0
4+	3	0.7
Total	450	100.0

*Degree of hypertrophy based on tables of normal weights of hearts correlated with body weight, as prepared by Smith.[142]

†In 76 cases the weights were not stated. In some the prosectors stated that the hearts were not enlarged. It is assumed that in the others, the prosectors considered that the hearts were not enlarged.

Correlation of Cardiac Hypertrophy With Various Factors.—There was no indication that cardiac hypertrophy is correlated with induction blood pressure, but the series provides too few cases to study this relationship very closely.

There was a previous history of cardiac disease, either definite or possible, in 34 per cent of the patients with hypertrophy of Grade 2 and over, as compared with 17 per cent of those with no hypertrophy or hypertrophy less than Grade 2.

There was a significantly high correlation between cardiac hypertrophy and the duration of the terminal illness. In only 11 per cent of the patients in whom the terminal illness lasted less than twenty-four hours was there cardiac hypertrophy of Grade 2 or more, whereas it was found in 33 per cent of the patients in whom the terminal illness lasted more than twenty-four hours. Similarly, 42 per cent of the men who had hypertrophy of Grade 2 or more lived longer than twenty-four hours, as compared with only 12 per cent of the men with no hypertrophy or hypertrophy less than Grade 2. These figures may indicate that hypertrophy is the result of a compensating mechanism which makes the heart somewhat better able to cope with insult.

There was found to be no significant difference in the proportion of patients with sclerotic occlusion among those with no cardiac hypertrophy or hypertrophy under Grade 2 and those with cardiac hypertrophy of Grade 2 or over. About one-half of the patients in each group had sclerotic occlusion somewhere in the left anterior descending artery, the left circumflex artery, or the right circumflex artery.

There was no significant difference in the proportion of patients in whom there was thrombotic occlusion among those with no cardiac hypertrophy or hypertrophy under Grade 2 and those with hypertrophy of Grade 2 and over. About one-half of the men in each group had thrombotic occlusion in one of the major coronary arteries.

The occurrence of myocardial infarcts, however, was definitely correlated with cardiac hypertrophy, since gross infarcts were found more than twice as frequently with cardiac hypertrophy of Grade 2 and over as when there was no cardiac hypertrophy or hypertrophy under Grade 2 (Table XXIX). Likewise,

TABLE XXIX. CARDIAC SIZE IN RELATION TO MYOCARDIAL INFARCTS AMONG MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

INFARCTS	DEGREE OF HYPERTROPHY			
	NORMAL SIZE OR HYPERTROPHY UNDER GRADE 2*		HYPERTROPHY GRADE 2 AND OVER	
	NO.	%	NO.	%
None	283	74.5	32	45.7
Gross	77	20.2	35	50.0
Microscopic	20	5.3	3	4.3
Total	380	100.0	70	100.0

*There were 76 hearts, the weights of which were not recorded, which were probably not appreciably enlarged.

myocardial scarring was more common in the group of patients with cardiac hypertrophy of Grade 2 and over than in the other group; the ratio was 72 to 55 per cent (Table XXX). There was also a significantly greater proportion of patients with mural thrombi among those with cardiac hypertrophy of Grade 2 and over than among those of the other group (21 per cent as against 8 per cent).

TABLE XXX. CARDIAC SIZE IN RELATION TO MYOCARDIAL SCARRING IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SCARRING	SIZE OF HEART					
	NORMAL SIZE OR HYPERTROPHY UNDER GRADE 2		HYPERTROPHY GRADE 2 AND OVER		HYPERTROPHY NOT STATED*	
	NO.	%	NO.	%	NO.	%
None	133	43.9	20	28.2	27	35.5
Diffuse	105	34.6	26	36.6	24	31.6
Focal	49	16.2	20	28.2	20	26.3
Diffuse and focal	10	3.3	5	7.0	2	2.6
Not stated	6	2.0	0	0.0	3	4.0
Total	303	100.0	71	100.0	76	100.0

*Probably little or none.

In four patients with old rheumatic valvulitis and in the one patient with syphilitic aortitis, there was hypertrophy of Grade 2 + to 4.

Vascular lesions in the kidneys did not influence the factor of cardiac hypertrophy, since the two findings were present in about the same percentage in each of the two groups (under Grade 2 and Grade 2 and over).

These facts tend to clarify the old controversy of whether coronary artery sclerosis or myocardial degeneration influences hypertrophy of the heart. There is a definite indication that myocardial degeneration does cause hypertrophy, since the hearts more seriously damaged by infarction or scarring and those with mural thrombi tended to be larger than those without these lesions but with coronary artery disease alone. The true explanation of this result is debatable. However, it may be that there is in the early stage of the disease a relative myocardial anoxia which reduces the tone of the myocardium and allows stretching of the fibers. Additional stretching would be likely to occur with each acute occlusion of one of the coronary arteries. Gradually, however, the collateral circulation might be built up in certain cases to the point where hypertrophy of myocardial fibers could occur.

When the literature is reviewed with reference to the question of coronary artery disease causing hypertrophy, one finds that criteria for hypertrophy are rarely given or that any weight over a certain number of grams is assumed to indicate hypertrophy, and that the presence or absence of hypertension as a factor is usually not clearly stated. The following are outstanding examples. Among Nathanson's[34] 113 cases, hearts weighing more than 400 grams were

considered to be enlarged, and in sixty-eight cases the hearts weighed more than that. Congestive failure was more common with large hearts (forty-six cases). Barnes and Ball[22] stated that in a series of forty-nine cases of infarction, the hearts tended to exceed average weights. Among 100 autopsied cases Lisa and Ring[45] found the average weight to be 519 grams, with a range of 200 to 925 grams; the cause of the hypertrophy was not apparent. Appelbaum and Nicholson[54] reported the heart weight in ninety-four of 150 cases and stated that the majority of hearts were above the average range; sixty-nine had weights greater than 400 grams. However, many patients had had hypertension, and the authors concluded that factors other than coronary artery sclerosis were responsible for the hypertrophy. Glendy and co-workers[62] studied a series of 100 patients under 40 years of age and 300 over 80 years of age. Of the 100 younger patients, 37 per cent had enlarged hearts. The authors stated that considerably more of the younger group had hearts of normal size. In a series of forty-eight cases, Woods and Barnes[143] found forty-five hearts to be enlarged, the average weight being 496 grams. These authors considered the average normal weight to be 330 grams. Bruenn and associates[92] found hypertrophy of the heart to exist in 236 (70 per cent) of 338 cases, the average weight being 543 grams. In Bean's[14] series of 300 cases hypertrophy was found in 84 per cent; hearts weighing more than 350 grams in women and 400 grams in men were considered to be hypertrophied. Bean concluded that the "majority of cases with cardiac infarction have enlarged hearts." In 1928 Parkinson and Bedford[40] concluded that "coronary artery disease alone can cause some degree of hypertrophy of the heart, especially of the left ventricle, but unless high blood pressure or valvular disease is present in addition, cardiac enlargement is not a feature." We believe that our study shows definitely that coronary artery disease alone may lead to hypertrophy. The explanation given by Davis and Blumgart[145] is in line with what we believe to be probable. These authors postulated that with severe coronary sclerosis some hypertrophy results from impaired nutrition which causes the myocardial fibers to stretch and that the hypertrophy is greater in cases of congestive failure.

Dilatation of Hearts.—There was no significant dilatation of the chambers of the hearts in 360 (80 per cent) of the patients. Dilatation was slight or just noticeable in forty-two patients (9 per cent), moderate in twenty-four (5 per cent), and great in six (1 per cent). In some other patients dilatation of the right auricle and/or ventricle was noted, but unless this was great, the case was not included in the figures.

Myocardial Infarcts.—Gross infarcts were present in 114 patients. In sixteen patients there were two gross infarcts. Microscopic infarcts were present in twenty-three other patients, making a total of 137 patients with infarcts and a total of 153 infarcts. The locations of the infarcts, both gross and microscopic, are tabulated in Table XXXI. They were in the left ventricle and/or interventricular septum, left side, in all but seven patients, in whom they were in the posterior wall of the right ventricle. There were recent or fresh gross infarcts in sixty-eight patients, organizing gross infarcts in twenty-two, and old

gross infarcts in thirty-four; in six the age of the gross infarct was not noted. In thirty-one of the patients in whom the size of the gross infarcts was given, the diameter was from 0.5 to 1.9 cm., in sixteen it was from 2.0 to 3.9 cm., in six it was from 4.0 to 5.9 cm., and in six it was 6.0 cm. or more.

TABLE XXXI. LOCATION OF MYOCARDIAL INFARCTS (GROSS AND MICROSCOPIC) IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION	NO.	%
Left ventricle, without localization	41	26.7
Left ventricle, anterior wall	34	22.2
Left ventricle, apex and interventricular septum	21	13.7
Interventricular septum, anterior third	14	9.2
Left ventricle, apex	13	8.5
Left ventricle, posterior wall	12	7.9
Interventricular septum, posterior upper part	6	3.9
Left ventricle, lateral wall	5	3.3
Right ventricle, posterior wall	7	4.6
Total	153	100.0

*There were 112 patients with gross and twenty-three patients with microscopic infarcts. In fourteen patients there were two infarcts and in two there were three infarcts. The infarcts were recent or fresh in ninety-two patients, organizing in twenty-three, and old in thirty-two; in six the age was not stated.

Myocardial Scarring.—Scars were present in the myocardium of 261 hearts, being diffuse in 155, focal in eighty nine, and diffuse and focal in seventeen. The exact extent of scarring was not definite, since usually only a few areas were examined microscopically.

State of the Coronary Arteries.—Due allowances must be made for the fact that many prosectors do not adequately examine all parts of the subepicardial coronary arteries. Sometimes they proceed no farther after finding some areas indicating disease. In forty-six patients the arteries showed neither sclerotic nor thrombotic occlusion but only thickening of the walls and narrowing of the lumina. It is quite possible that a diligent search might have uncovered more severe lesions, since these were unquestionably patients in whom death was the result of coronary artery disease, proved by clinical observations and by the absence of any other adequate cause of death; furthermore, in eight of these forty-six patients there were gross myocardial infarcts.

In 232 patients there was almost complete sclerotic occlusion in some part or parts of one or more coronary arteries, distributed as shown in Table XXXII. Here it is seen that the great preponderance of occlusions was in the proximal one-third of the left anterior descending artery. It must be pointed out, however, that various combinations existed. There was practically complete sclerotic occlusion of all three vessels in eighteen patients, of the left anterior descending and the left circumflex arteries in twenty-one, of the left anterior descending and right coronary arteries in nineteen, and of the left circumflex and right coronary arteries in two. In 229 patients there was thrombotic occlusion, recent, or-

ganizing, or old, in some part or parts of one or more coronary arteries, distributed as shown in Table XXXIII. Here, again, the occlusion was most often in the left anterior descending artery. There was, however, a difference in the distribution of the two forms of occlusion in the left circumflex artery, sclerotic occlusion existing in that artery in sixty patients, but thrombotic occlusion in only twenty-eight. In fifty-seven patients both sclerotic and thrombotic occlusions were present. Therefore, the totals were: sclerotic occlusion alone in 175

TABLE XXXII. ALMOST COMPLETE SCLEROTIC OCCLUSION OF CORONARY ARTERIES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION WITHIN ARTERY	CORONARY ARTERIES		
	LEFT ANTERIOR DESCENDING	RIGHT CORONARY	LEFT CIRCUMFLEX
Proximal alone	128	33	41
Medial alone	3	3	1
Distal alone	1	0	0
Proximal and medial	40	15	9
Proximal and distal	0	0	0
Medial and distal	0	0	0
Proximal, medial, and distal	8	4	3
Undifferentiated	12	4	6
Total	192	59	60

*Of these the following combinations existed: left anterior descending and left circumflex, 21 cases; left anterior descending and right coronary, 19 cases; left anterior descending, left circumflex, and right coronary, 18 cases; left circumflex and right coronary, 3 cases.

TABLE XXXIII. THROMBOTIC OCCLUSION OF CORONARY ARTERIES IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE*

LOCATION WITHIN ARTERY	CORONARY ARTERIES		
	LEFT ANTERIOR DESCENDING†	RIGHT CORONARY†	LEFT CIRCUMFLEX†
Proximal alone	129	34	20
Medial alone	7	4	1
Distal alone	2	0	0
Proximal and medial	23	7	5
Proximal and distal	0	0	0
Medial and distal	1	0	0
Proximal, medial, and distal	3	1	0
Undifferentiated	9	3	2
Total	174	49	28

*Of these the following multiple thrombi occurred, one in each location: left anterior descending and right coronary, nine; left anterior descending and left circumflex, four; right coronary and left circumflex, three; all three arteries, three.

†Thrombotic occlusion occurred in 229 cases. The thrombus was recent or fresh in 156 cases, organizing in nineteen, old in twenty, both old and fresh in twelve, and of unstated age in twenty-two.

patients; thrombotic occlusion alone* in 172; both sclerotic and thrombotic occlusion in fifty-seven. The thrombus was recent or fresh in 156 patients, organizing in nineteen, old in twenty, both old and fresh in twelve, and of unstated age in twenty-two.

From these figures, therefore, one is forced to conclude that coronary artery occlusion, both sclerotic and thrombotic, is greatly predominant in the left anterior descending artery, at least in this age group and probably in other age groups. This conclusion is in agreement with that of most authors[33,40,45,102,141]; the conclusion of Barnes and Ball[22] was the notable exception. Among our group of survivors, however, posterior infarctions were more than one-half as frequent as anterior infarction (28 per cent as compared with 44 per cent); there may be some justification, therefore, in the statement by some authors that acute occlusion of the right coronary artery carries a better prognosis than that of the left anterior descending artery. Our observations also confirm those of Saphir and associates,[133] who found the three main coronary arteries always involved by atherosclerosis. This was true, on the whole, in our series, although there were some exceptions. There were no cases of a single atheroma causing occlusion or being the site of the thrombus.

A summary of the pathogenesis of "coronary deaths" is given in Table XXXIV. This shows that 336 men died of coronary insufficiency without gross

TABLE XXXIV. SUMMARY OF PATHOGENESIS OF DEATHS FROM CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

OCCLUSION	NO.	%
Patients without gross myocardial infarction	336	100.0
Without occlusion, sclerotic or thrombotic	38	11.3
With sclerotic occlusion alone	148	44.1
With thrombotic occlusion alone	117	34.8
With sclerotic and thrombotic occlusion	33	9.8
Patients with gross myocardial infarction*	114	100.0
Without occlusion, sclerotic or thrombotic	8	7.0
With sclerotic occlusion alone	27	23.7
With thrombotic occlusion alone	55	48.2
With sclerotic and thrombotic occlusion	24	21.1

*The age distribution of the infarcts was as follows: recent or fresh infarcts in fifty-six patients, one each; organizing infarcts in twelve patients, one each; old or healed infarcts in twenty-four patients, one each; one recent and one organizing infarct in each of six patients; one recent and one old infarct in each of six patients; one organizing and one old infarct in each of four patients; and one infarct of unstated age in each of six patients.

myocardial infarction, and that 114 died after the formation of gross infarcts. Death resulted from coronary insufficiency without gross infarction or coronary occlusion in thirty-eight patients. Gross infarcts were present in eight men without coronary artery occlusion. Gross infarcts were much more frequent with thrombotic occlusion and thrombotic and sclerotic occlusion combined, than with sclerotic occlusion alone. The number of deaths in the patients without gross infarction was greater with sclerotic occlusion alone than with the total of

*The thrombus forming, of course, in sclerotic vessels.

thrombotic occlusions and thrombotic and sclerotic occlusions combined. The possibility of spasms of the collateral and unaffected smaller coronary arteries in the production of coronary insufficiency and angina pectoris, as postulated by Leary[146] and Gilbert,[147] cannot be confirmed or denied in morphologic studies such as this. It will be very difficult to settle this point; we are inclined to doubt that the factor of spasm is important in most cases. On the other hand, the results of the study of this series are in line with the work and conclusions of Blumgart, Schlesinger, and Davis[118] and Blumgart, Schlesinger, and Zoll.[123] Although the injection method of examination was not used in this series, the fact that in about one-half of the patients who died there were no known symptoms prior to the fatal attack, in spite of advanced artery disease, leads one to think that intercoronary communication of importance probably had developed.

The large number of coronary deaths without infarction in our series stimulated us to look up the literature on this subject. Among twenty-three cases studied by Wolff and White,[1] six of the patients died as the result of coronary artery occlusion without infarction. Appelbaum and Nicholson[54] had thirteen such patients among 150 cases of occlusion. Wright-Smith[58] reported a series of 495 cases of coronary artery occlusion with only eighty-seven infarctions; 224 of the cases were instances of sudden death. Benson[64] presented a case report of a 34-year-old pilot who suffered an attack of acute chest pain while flying and died twenty minutes after landing the plane; autopsy revealed atherosclerosis of both right and left coronary arteries, but there was no acute occlusion and no infarction. Jokl and Melzer[70] reported twenty cases of sudden death due to cardiac causes; four of the patients showed marked coronary artery sclerosis without infarction. Levy and Bruenn[93] studied twenty-four cases of coronary death selected on the basis of coronary sclerosis without thrombosis.

Coronary insufficiency without thrombosis of a coronary artery is not uncommon. In the series of 150 cases of Appelbaum and Nicholson,[54] there were thirty-seven patients with marked sclerotic narrowing but without coronary thrombosis in which an infarct was encountered. Nathanson[34] observed only twenty-four of 113 patients with fatal coronary artery disease in whom a coronary thrombus was found. Lisa and Ring[45] noted coronary thrombosis in thirteen of thirty-two patients with fresh myocardial infarction; among sixty-eight patients with healed infarcts, coronary thrombosis was recognized in eleven. In the study of 495 cases by Wright-Smith[58] there were 339 coroner's cases, in 314 of which (92.9 per cent) there was atheromatous occlusion and in only twenty-four (7 per cent), coronary artery thrombosis. Of his 156 hospitalized patients, 135 (86.6 per cent) had atherosclerotic occlusion and twenty-one (13.4 per cent), thrombotic occlusion. In Bean's[144] series of 300 cases, 20 per cent of the patients (with fifty-eight infarcts) had arterial narrowing without thrombosis. Gross and Sternberg[149] reported fifteen cases of myocardial infarction without demonstrable occlusion of the coronary arteries. In a study of 153 cases of myocardial infarction, infarction in the absence of thrombotic occlusion occurred in thirty-seven patients; there were six patients in whom the only pathologic feature to which infarction could be ascribed was severe narrowing of the coronary arteries. Meesen[84] reported two series of cases of sudden death due to heart disease. In

one series there were 475 patients, of whom 188 had coronary sclerosis with thrombosis and 287 had sclerosis without thrombosis. The second series was made up of 115 cases, in which there were forty-nine patients with coronary sclerosis with thrombosis and sixty-six with sclerosis without thrombosis.

Nathanson[34] sums up the situation well by stating that "A prolonged attack, consisting of initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis." He states further that it is more reasonable to regard thrombosis not as an entity but merely as one of the end results of coronary disease occurring in approximately 20 per cent of the cases. Our experience with this large group of younger men leads to a somewhat different, although, in general, similar conclusion. We find that sudden death without infarction is more common in those with sclerotic occlusion alone, but that death from coronary artery disease is associated with coronary thrombosis in about 50 per cent of the cases. Our series demonstrates, too, that myocardial infarction may occasionally result from ischemia due to coronary artery sclerosis without either sclerotic or thrombotic occlusion.

The Microscopic Lesions of the Coronary Arteries and Myocardium.—There was no difference in the histologic appearance of the coronary lesions in the patients of this series from those described many times as coronary arteriosclerosis. There were no clear-cut cases of thromboangiitis obliterans, periarteritis nodosa, or rheumatic arteritis.[150]

The atheromatous plaque was the prominent lesion which reduced the vascular lumen (Figs. 7 and 8). The plaques were more frequently eccentric than annular in disposition (Fig. 9). They usually had thin zones of mixed fibrous and collagenous connective tissue which rested on the remnants of the internal elastic lamina. Vascularization of the plaques, present to some extent in about one-half of the patients, was usually most prominent at their margins and bases (Fig. 10). The plaques frequently contained a central nidus of cholesterol crystals, lipophages of various forms, amorphous material, and occasionally fine granules of calcium (Figs. 11, 12, 13, 14, 15, and 16). Less frequently larger masses of calcium were encountered. These atheromatous deposits were covered by a zone of hyalinized connective tissue which outlined the remaining lumen. Occasionally the surface zone was composed of more cellular, vascular connective tissue in which small deposits of fibrinoid material were found. An endothelial lining was rarely demonstrable. The lumen in all patients was reduced, in many instances to the extent that there was little or no opening left.

After much study it was decided that sclerosis of the coronary arteries could be grouped into three grades on the basis of age of the disease, although there is no way of determining just how old the lesion is, since the degenerative process may develop faster in some patients than in others and since the rate of development may vary in different parts of the arterial tree. There is, of course, some overlapping of the various features. The classification is as follows:

GRADE 1. EARLY ATHEROSCLEROSIS (FIG. 17)

1. Simple plaque formation, the plaque being composed chiefly of moderately loosely arranged connective tissue frequently containing young fibroblasts
2. Absence of calcium
3. Presence only occasionally of a small nidus of amorphous material in the plaque
4. Slight, if any, vascularization of plaque or media
5. Few, if any, cholesterol crystals in the plaque
6. Slight to moderate damage to the internal elastic lamina, which usually may be identified
7. Slight thinning with minimal interstitial fibrosis of the media below the plaque

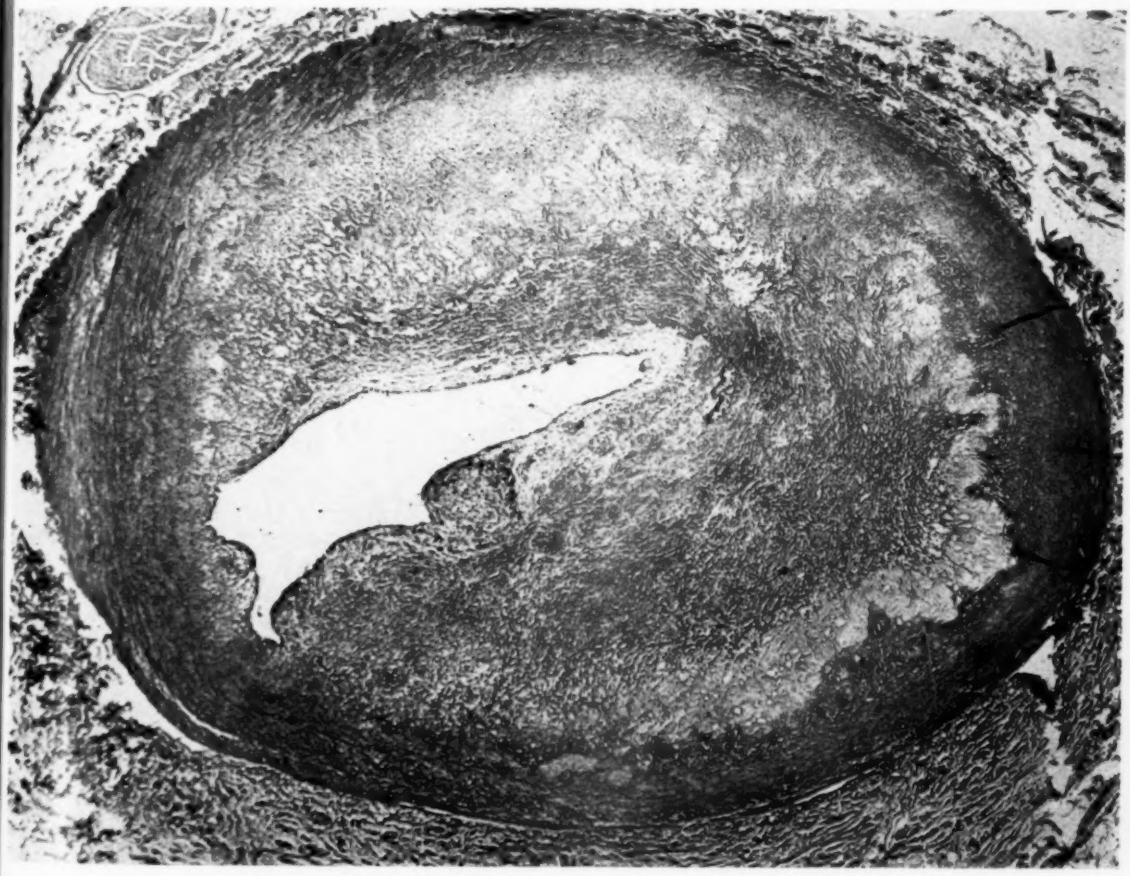

Fig. 7.—Cross section of anterior descending coronary artery in a man 22 years of age, showing great reduction in size of lumen resulting from the presence of a large atheromatous plaque. Reduced from a magnification of × 32. A.I.P. Neg. 94354.

GRADE 2. MODERATELY ADVANCED ATHEROSCLEROSIS (FIG. 9)

1. Hyalinized base of the plaque
2. Presence of a large mass of amorphous cholesterol or lipid in the plaque
3. Surface of plaque composed of compact fibrous tissue in which a few fibroblasts persist
4. Minimal calcium deposition in center of plaque usually in the form of fine calcium granules or calcified nuclei of fibroblasts
5. Presence of a few cholesterol clefts
6. Slight marginal vascularization
7. Fragmentation or frequent absence of internal elastic lamina
8. Moderately thin, occasionally vascularized media, with loss of muscle fibers and increased fibrosis below plaque

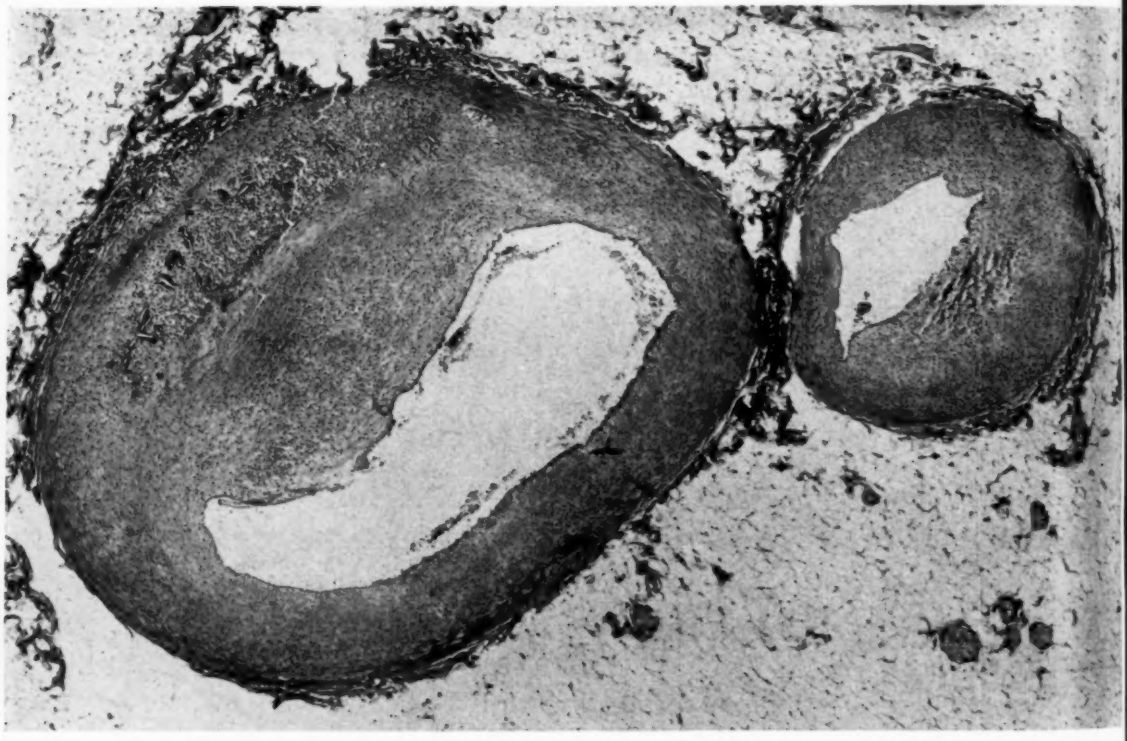

Fig. 8.—Sclerosis of coronary artery and a secondary branch (simple narrowing), showing that coronary artery disease is generalized, a not uncommon finding. Man 34 years of age. Reduced from a magnification of × 30. A.I.P. Neg. 94231.

GRADE 3. ADVANCED ATHEROSCLEROSIS (FIG. 11)

1. Complete or almost complete hyalinization of the plaque, both base and surface zones, with fibroblasts remaining only at margins
2. Masses of calcium in plaques
3. Frequent presence of cholesterol clefts
4. Common presence of broad vascular channels at margin and base of plaque
5. Absence of or severe damage to internal elastic lamina
6. Hyalinization or atrophy of media, with loss of muscle and increase in fibrous tissue

GENERAL OBSERVATIONS

1. Size of plaque bears little relation to age of lesion
2. Cellular infiltration with lymphocytes and plasma cells either in plaque or adventitia bears little relation to age of lesion, although it is slightly more common in the younger lesions.

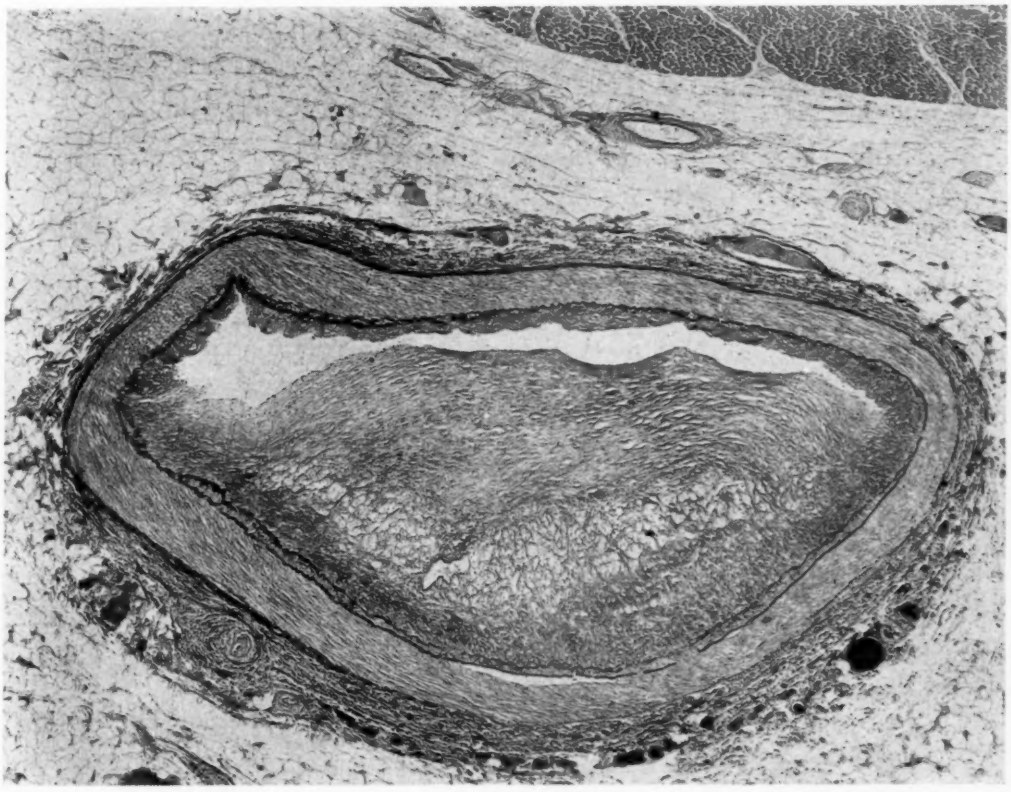

Fig. 9.—Large eccentric atheromatous plaque in coronary artery of a man 23 years of age (Grade II atherosclerosis). Weigert's elastic tissue stain. Reduced from a magnification of × 30. A.I.P. Neg. 94236.

Table XXXV shows the distribution of the three grades of atherosclerosis on the basis of this classification among 308 patients, compared with 151 patients of a 40- to 49-year age group. This table shows well how the age of the atherosclerosis advances with the ages of the patients according to the method of grading adopted. This method of gradation is somewhat at variance with that of Leary,[48,151,152,153] but it appeals to us as being more logical, since the degenerative changes of the media definitely progress as our grades of atheromatosis advance. Thus, actually from the changes of the media one is able to establish the relative age of the atheromatous plaque.

TABLE XXXV. DISTRIBUTION OF GRADES OF ATHEROSCLEROSIS BY AGE GROUP OF PATIENTS

GRADE OF ATHEROSCLEROSIS	AGE GROUPS									
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS		40 TO 49 YEARS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I	17	68.0	39	66.1	26	27.4	9	7.0	1	0.7
II	5	20.0	9	15.3	46	48.4	33	25.6	36	23.8
III	3	12.0	11	18.6	23	24.2	87	67.4	114	75.5
No. of Cases	25		59		95		129		151	

Note: Grade II includes one patient in the 18- to 24-year age group, two in the 25- to 29-year age group with both Grades I and II, and Grade III includes sixteen patients in the 40- to 49-year age group with both Grades II and III, and one patient with Grades I, II, and III. The total number of patients compared is, therefore, 459.

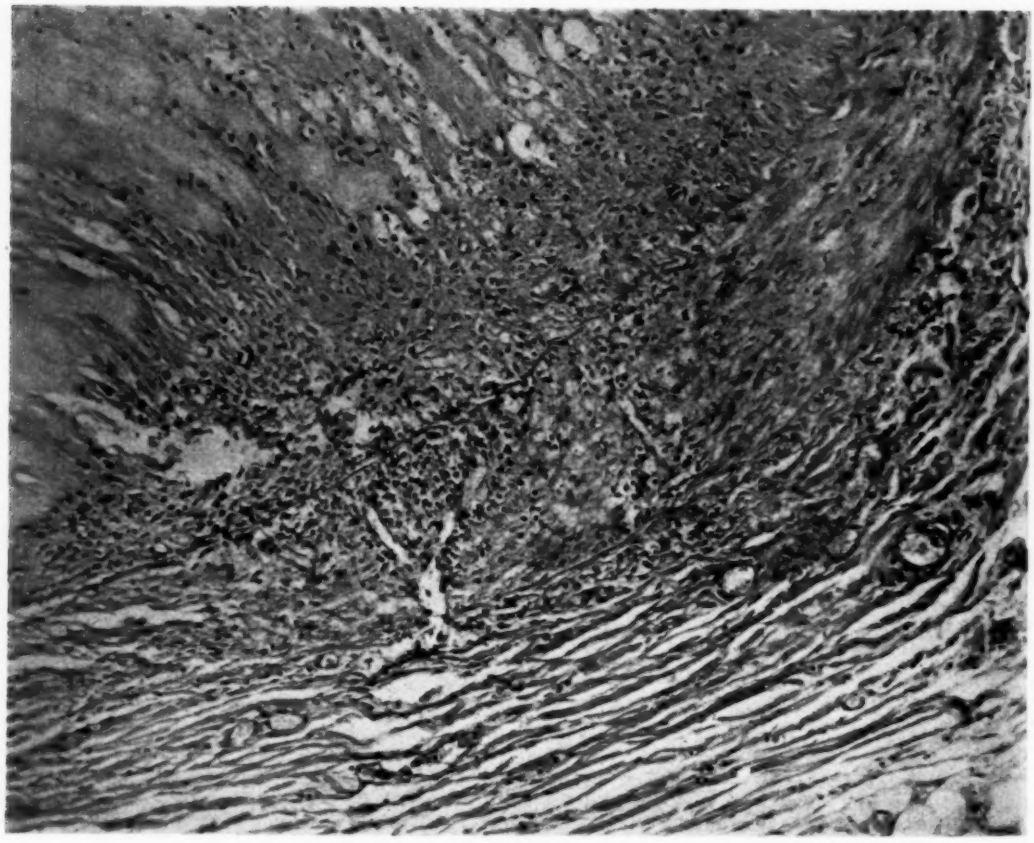

Fig. 10.—Vascularization of atheromatous plaque from fibrotic media of coronary artery of man 30 years of age. Reduced from a magnification of × 110. A.I.P. Neg. 94235.

It seems to us that one must preserve an open mind as to the importance of disturbance of cholesterol metabolism in the pathogenesis of atheroma. There is still the possibility that the deposition of lipids in the plaque is secondary rather than primary. As our material seems to show, the first stage in the life history of the atheromatous plaque is mainly that of fibroblastic proliferation of the intima; the second stage, the deposition of lipids and their ingestion and liquefaction by macrophages; and the third stage, hyalinization, with remnants of lipids in the form of cholesterol crystals remaining. Leary's excellent work, however, even though the conclusions may not be final, has done much to stimulate thought and study of the problem of atherosclerosis.

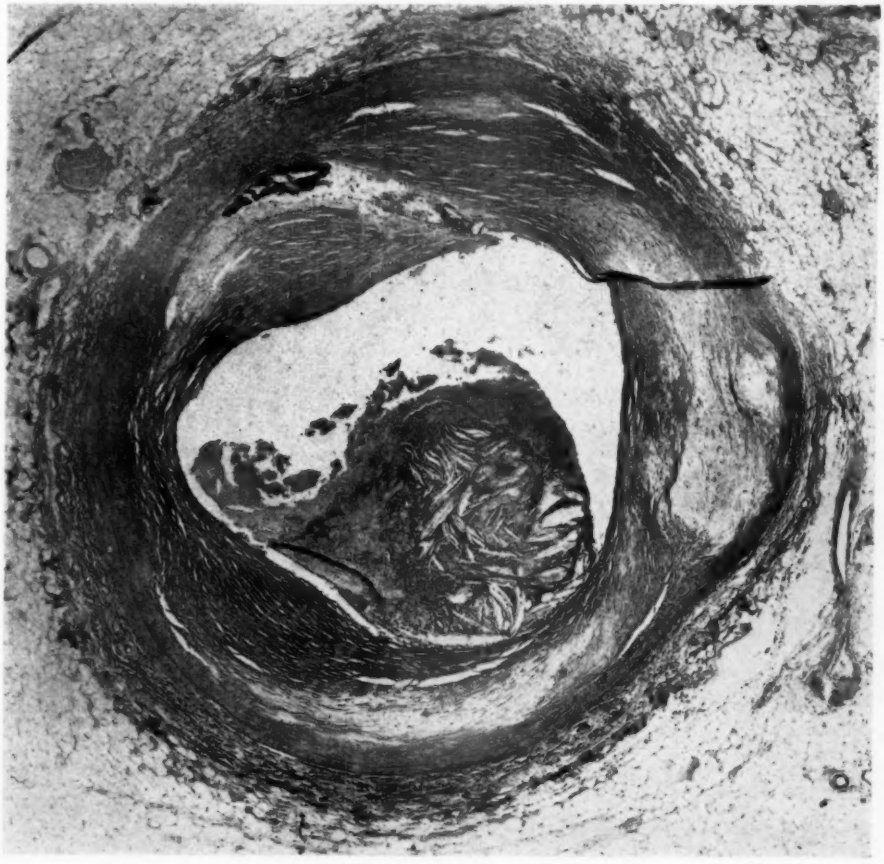

Fig. 11.—Atheromatous plaque with central nidus of cholesterol clefts in a man 36 years of age (Grade III atherosclerosis). Reduced from a magnification of × 30. A.I.P. Neg. 94233.

In approximately 35 per cent of the patients of this series recent thrombotic occlusion of the persisting lumen occurred (Figs. 18 and 19). In approximately another 9 per cent the thrombus was undergoing organization or was so old that it was a mass of scar tissue (Figs. 20, 21, and 22). Some of these thrombi were

Fig. 12.—Cholesterol clefts in plaque shown in Fig. 5, reduced from a magnification of ×110. A.I.P. Neg. 94234.

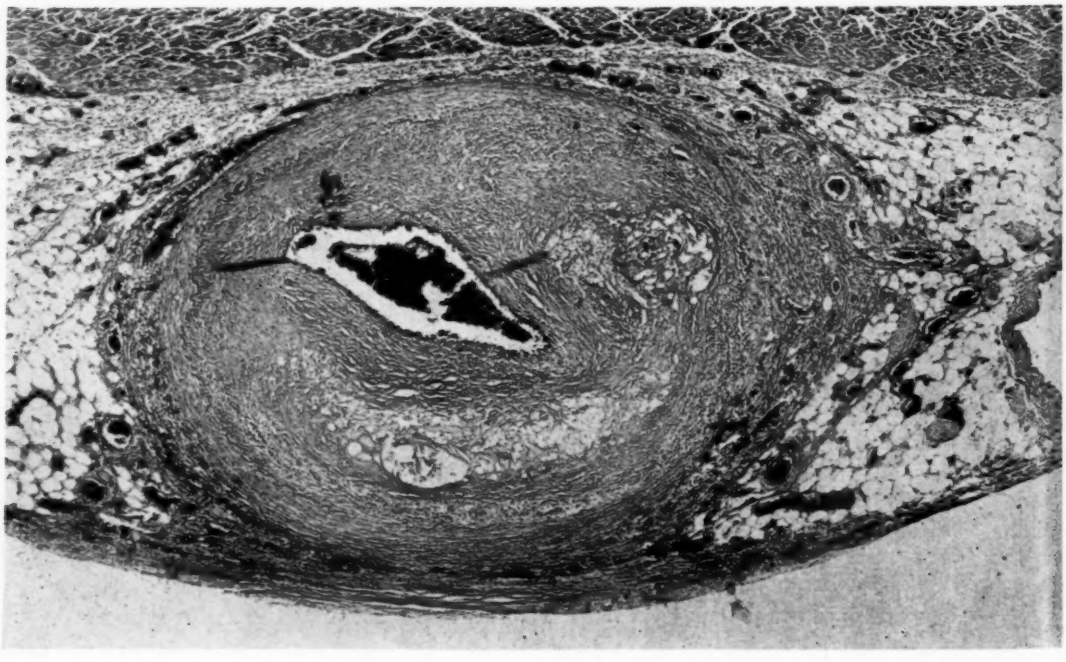

Fig. 13.—Coronary artery of a man 30 years of age, showing so-called atheromatous abscess. Reduced from a magnification of × 35. A.I.P. Neg. 94240.

recanalized, but the channels were so tortuous that only an insignificant column of blood could have passed through them (Figs. 23 and 24).

Below the site of plaque formation the internal elastic lamina was usually fragmented, reduplicated, ironed out, or completely absent, and the media was thin and atrophic. Infiltration of the media by round cells, chiefly lymphocytes, was rare (Fig. 25). There was slight to moderate adventitial fibrosis, most pronounced in that segment directly related to the position of the plaque. Occasionally there was moderate to dense infiltration of the adventitia by mononuclear cells, chiefly lymphocytes, but occasionally plasma cells.

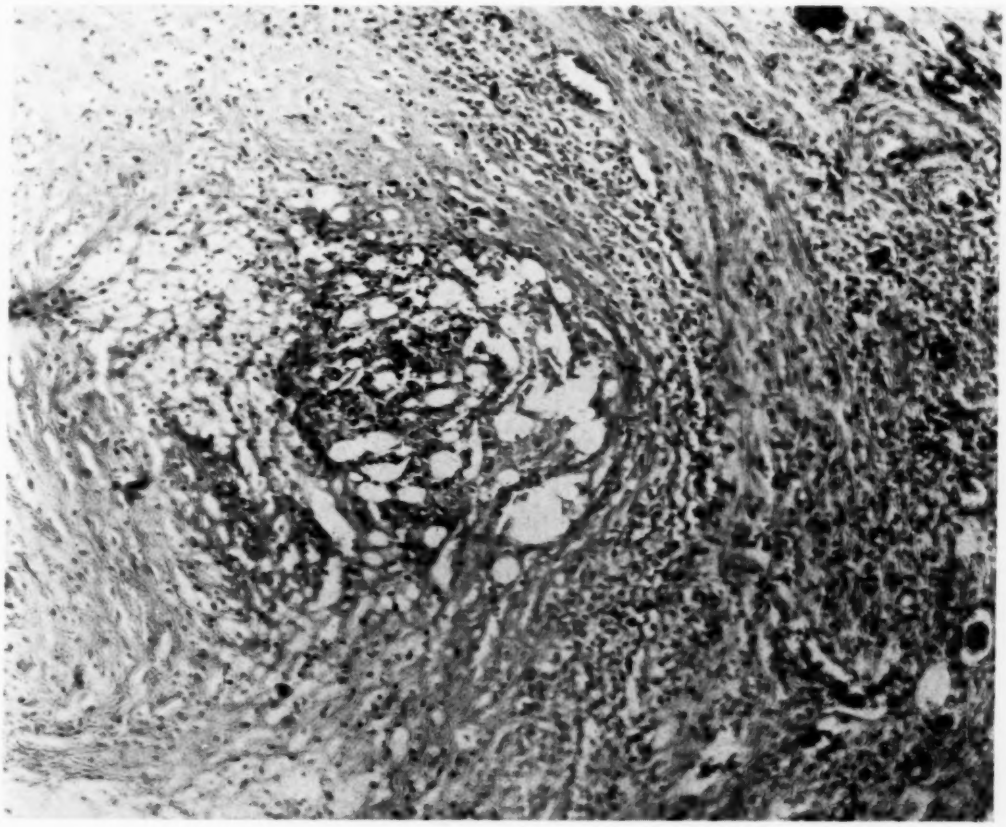

Fig. 14.—High-power view of so-called atheromatous abscess of artery shown in Fig. 7. Note lipophages and mononuclear infiltration. Reduced from a magnification of × 30. A.I.P. Neg. 94241.

Recent hemorrhage (Fig. 26) in the plaque was found in twenty-six patients (5.8 per cent) and old hemorrhage in twenty-nine (6.4 per cent). Both fresh and old hemorrhages were present in five of these. The incidence of hemorrhage in the plaque was much less than that given in the literature by Winternitz and associates,[154] by Wartman,[155] by Paterson,[156] by Horn and Finkelstein,[157] and by Field.[158] From our experience, therefore, we have not been impressed with the

importance of intramural hemorrhage, but it must be admitted that had serial sections of the vessels been studied, more cases of such hemorrhage might have been found. Also, we found that in the younger age groups there were fewer instances of the more advanced atheromatous lesions, and that there was a high incidence of deaths from coronary insufficiency without thrombosis. Table XXXVI shows the salient data of the coronary arteries as to the presence and age of thrombi, hemorrhage in, and rupture in the plaque according to age groups. This table shows insignificant differences in these factors in the different age groups up to 50 years.

Fig. 15.—Atheromatous plaque with large nidus of amorphous material and small eccentric lumen (practically complete sclerotic occlusion). Man 29 years of age. Reduced from a magnification of ×30. A.I.P. Neg. 94115.

The myocardial lesions were variable in degree and age. Recent infarctions grossly resembled those commonly described. The areas of recent gross infarction were pale gray or yellowish gray, soft, and granular, and on section stood slightly above the adjacent pinkish gray or russet brown myocardium.

TABLE XXXVI. CORONARY THROMBI, HEMORRHAGE IN PLAQUE, AND RUPTURE IN PLAQUE BY AGE GROUPS IN HEARTS EXAMINED MICROSCOPICALLY

LESION	AGE GROUP									
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS		40 TO 49* YEARS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Recent thrombus	9	36.0	12	20.3	23	24.2	28	21.7	45	29.0
Organizing or old thrombus	4	16.0	6	10.2	12	12.6	16	12.4	15	9.7
Total number with data	25		59		95		129		155	
Hemorrhage in plaque	4	16.0	11	18.6	16	16.8	20	15.5	20	13.0
Total number with data	25		59		95		129		154	
Rupture in plaque	0	0.0	0	0.0	4	4.2	10	7.8	6	5.8
Total number with data	25		59		95		129		103	

*The 40- to 49-year age group includes eight patients with both recent and old and one patient with both recent and organizing thrombi.

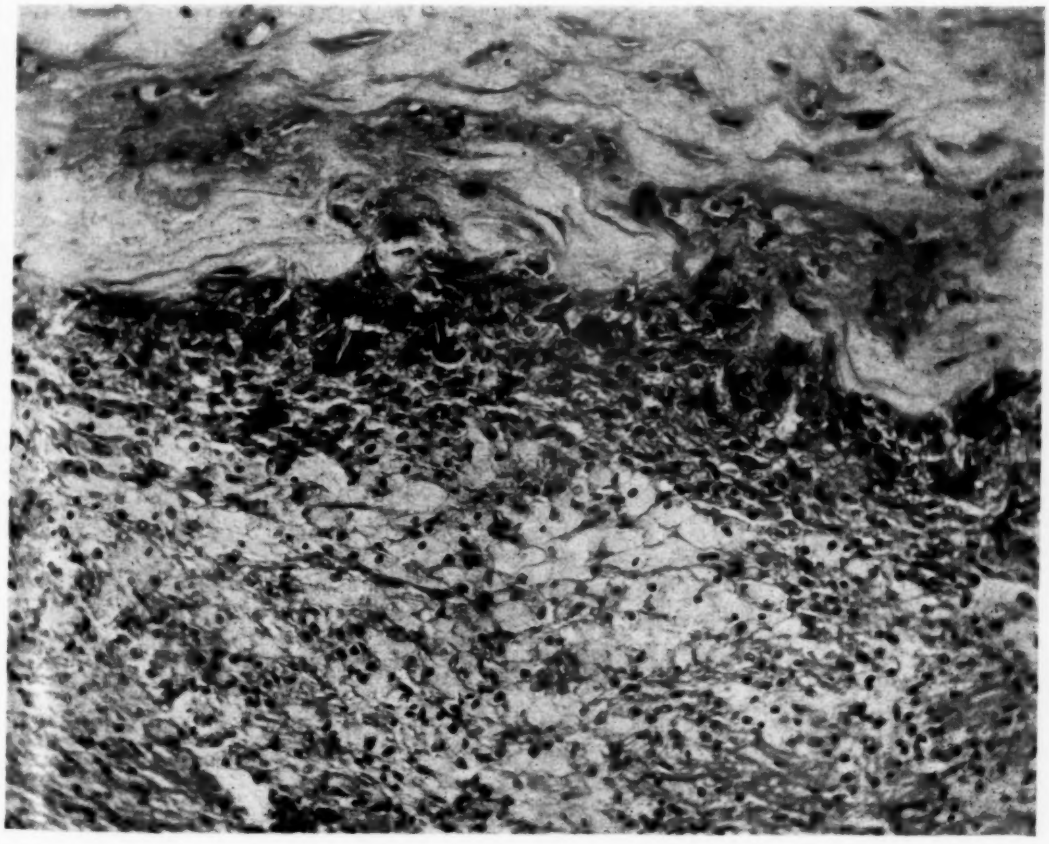

Fig. 16.—Section through fibrotic media (above) and edge of plaque, with deposits of calcium at base of plaque and lipophages (below). Man 35 years of age. Reduced from a magnification of × 235. A.I.P. Neg. 94218.

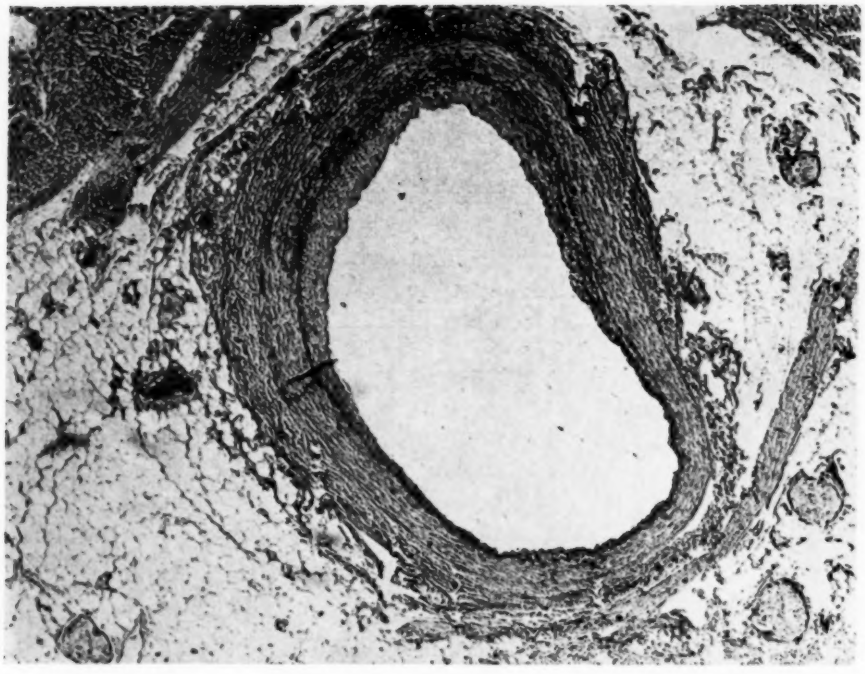

Fig. 17.—Grade I atherosclerosis. Man 23 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 100253.

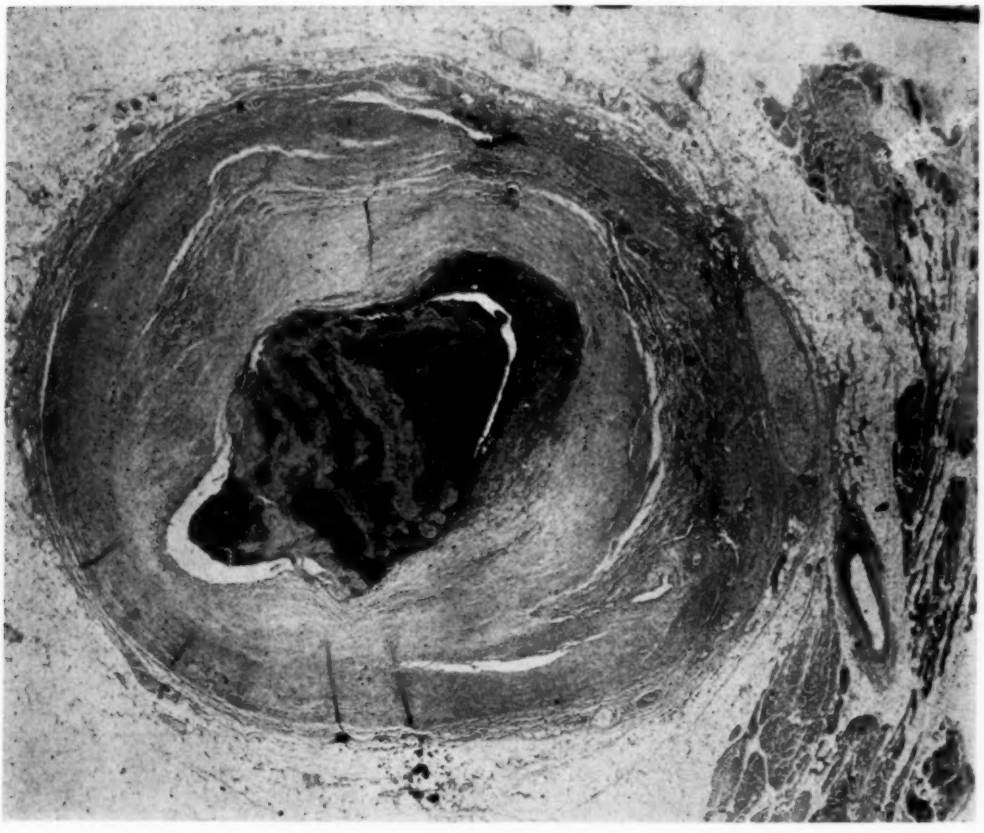

Fig. 18.—Fresh thrombus filling reduced lumen of sclerotic coronary artery of man 24 years of age. Reduced from a magnification of × 16. A.I.P. Neg. 94244.

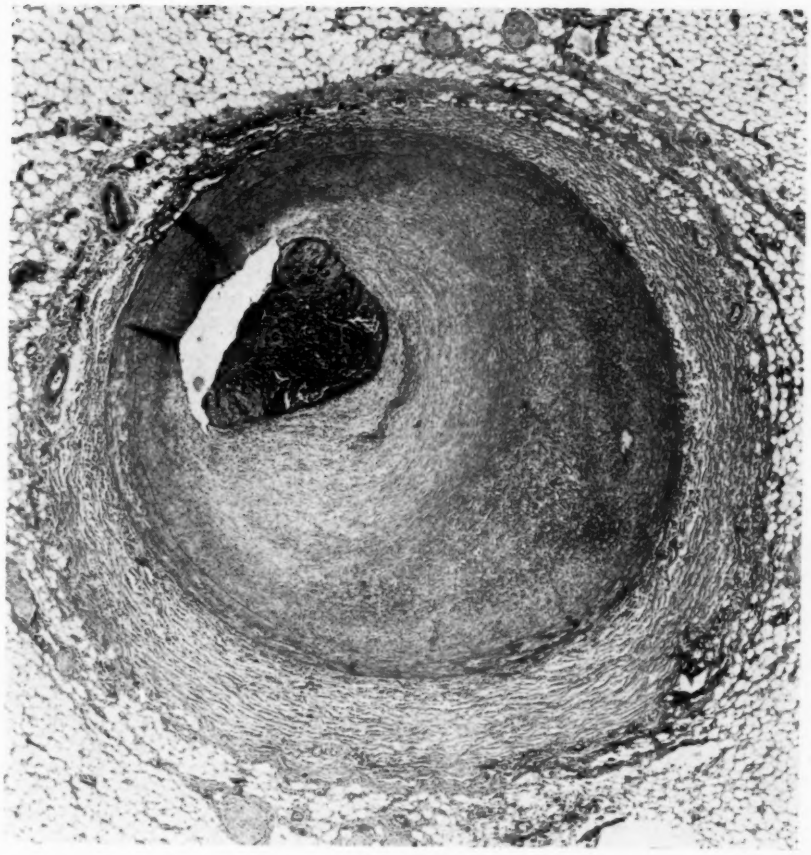

Fig. 19.—Fresh thrombus filling small lumen of sclerotic coronary artery of man 35 years of age. Reduced from a magnification of × 26. A.I.P. Neg. 94229.

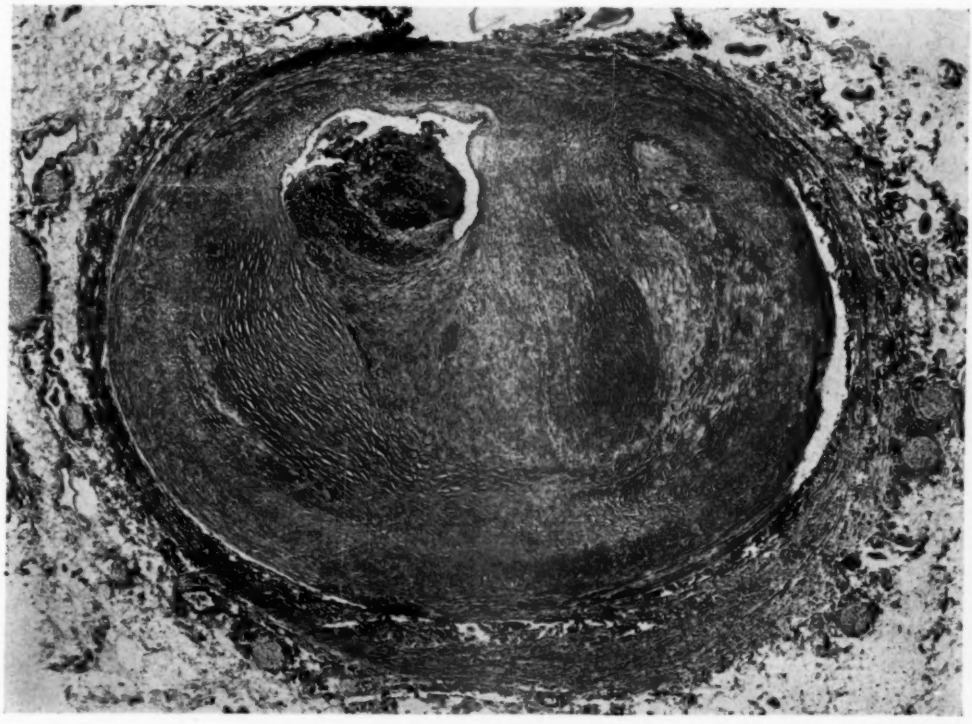

Fig. 20.—Organizing thrombus filling small lumen of sclerotic coronary artery of man 30 years of age. Note adventitial fibrosis. Reduced from a magnification of × 25. A.I.P. Neg. 94237.

Organizing gross infarcts were light gray, semitranslucent, and moderately firm, and frequently exhibited patchy zones which were slightly sunken or depressed. Gray trabeculations were interspersed by sunken zones which appeared slightly gelatinous in character.

Old gross infarcts were of firm, opaque, white fibrous tissue, usually slightly depressed, and frequently sending fibrous trabeculations into the adjacent myocardium.

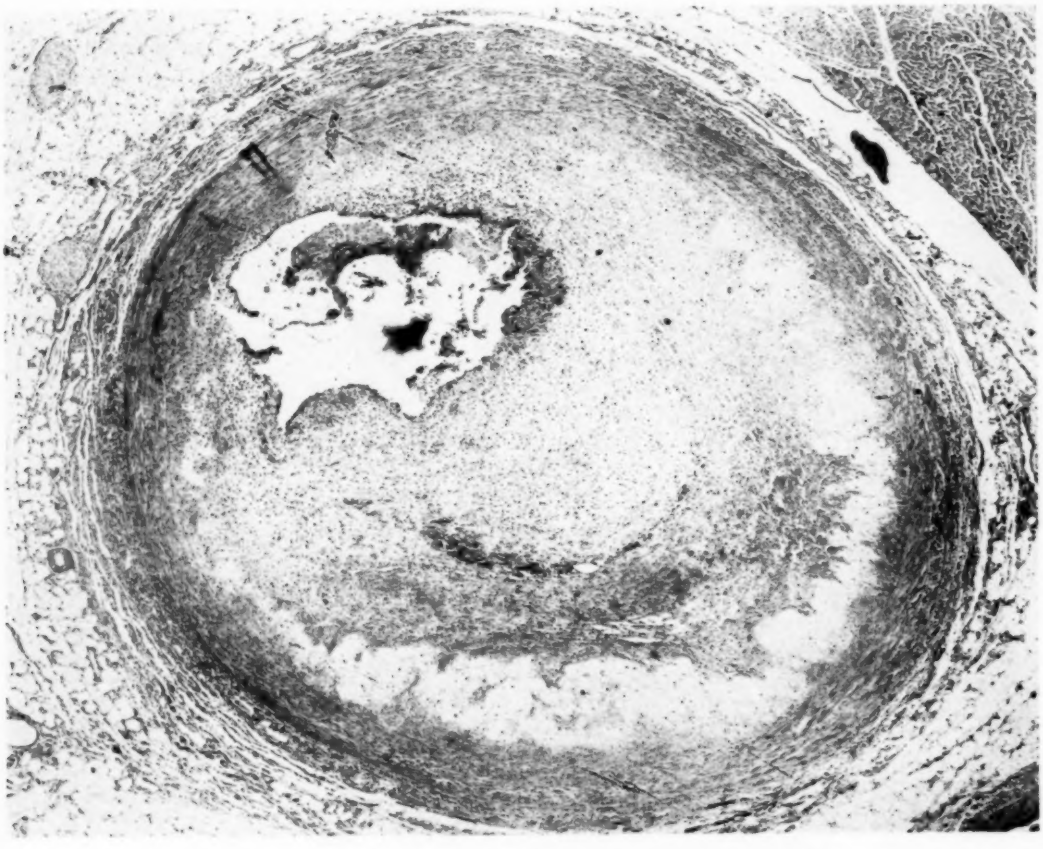

Fig. 21.—Organizing thrombus in lumen of sclerotic coronary artery of man 25 years of age. Note semilunar zone of amorphous material near base of plaque. Reduced from a magnification of × 25. A.I.P. Neg. 94222.

Microscopically, in recent infarctions there was necrosis of the myocardial fibers, pyknosis, karyorrhexis or karyolysis of nuclei, and dense infiltration of the area by polymorphonuclear leucocytes.

In organizing infarctions there was deposition of cellular fibrous connective tissue which was well vascularized by recently formed capillaries and sparsely infiltrated by mononuclear cells and phagocytes. Some of the adjacent viable fibers were hypertrophied. The arteries and arterioles frequently showed medial

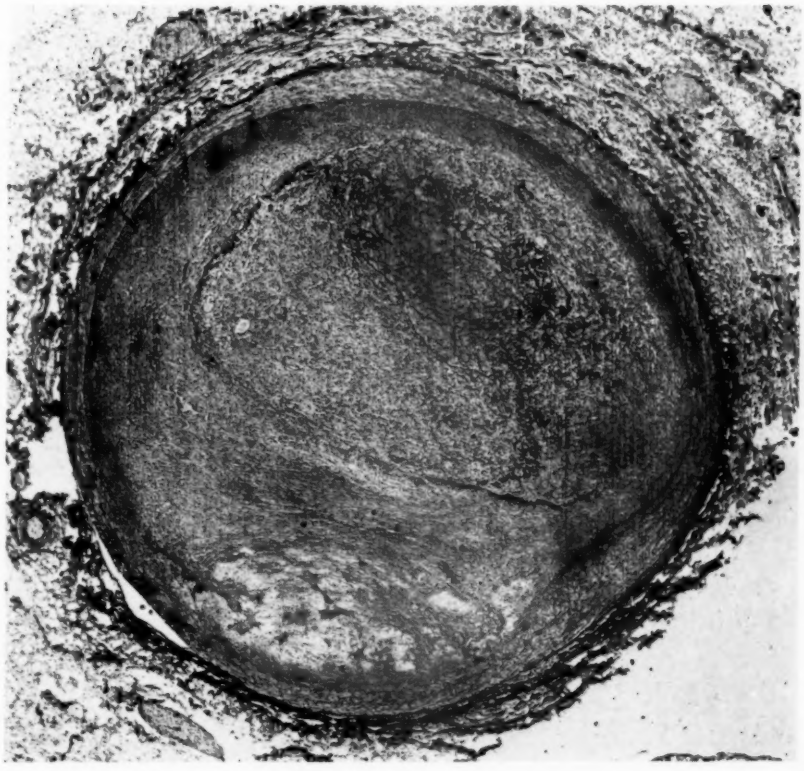

Fig. 22.—Organized thrombus filling lumen of sclerotic coronary artery of man 39 years of age. Reduced from a magnification of × 20. A.I.P. Neg. 94243.

hypertrophy in the zones of infarction, but they were rarely occluded by thrombi and never sclerotic.

In old infarcts there was replacement of broad zones of myocardial fibers by dense hyalinized fibrous tissue. Occasionally, sparse mononuclear leucocytic infiltration occurred in the region of these scars.

Table XXXVII shows the distribution of infarcts, recent, organizing, and old, diffuse fibrosis, focal scars, and mural thrombi in a special histologic study of the various age groups, including a 40- to 49-year age group.

Mural Thrombi.—Mural thrombi were present in forty-three patients: thirty-seven in the left ventricle, five in the right, and two in both. They ranged in size from less than 0.5 cm. to more than 6 cm. in diameter. They were responsible for hemiplegia in three patients at the clinical onset of the terminal illness and for five more clinically recognizable embolizations during the course of the illness.

The percentage of mural thrombi in this series is somewhat lower than that usually found in cases involving all ages, the average figures being 45 per cent.[144] Based on the 114 cases of gross myocardial infarction in this series, the percentage

TABLE XXXVII. MYOCARDIAL INFARCTS, DIFFUSE FIBROSIS, FOCAL SCARS, AND MURAL THROMBI AMONG DIFFERENT AGE GROUPS, IN HEARTS EXAMINED MICROSCOPICALLY

LESION	AGE GROUP									
	18 TO 24 YEARS		25 TO 29 YEARS		30 TO 34 YEARS		35 TO 39 YEARS		40 TO 49 YEARS	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Infarcts	8	32	14	24	26	27	40	31	76	44
Recent	4	16	4	7	6	6	13	10	37	21
Organizing	3	12	7	12	14	15	16	12	14	8
Old	1	4	3	5	6	6	11	9	11	6
Diffuse fibrosis	2	8	6	10	16	17	14	11	56	32
Focal scars	3	12	12	20	23	24	29	23	83	18
Mural thrombus	2	8	2	3	4	4	5	4	24	30
Total number with data	25		59		95		129		174	

The 30- to 39-year age group includes three patients with both recent and old, seven with recent and organizing, and four with organizing and old infarcts.

In the 40- to 49-year age group, the corresponding figures were: eight recent and organizing, one organizing and old, and two recent, organizing, and old infarcts.

The total number of infarcts found was seventy-six, but the age of infarct was not determined in fourteen of the patients.

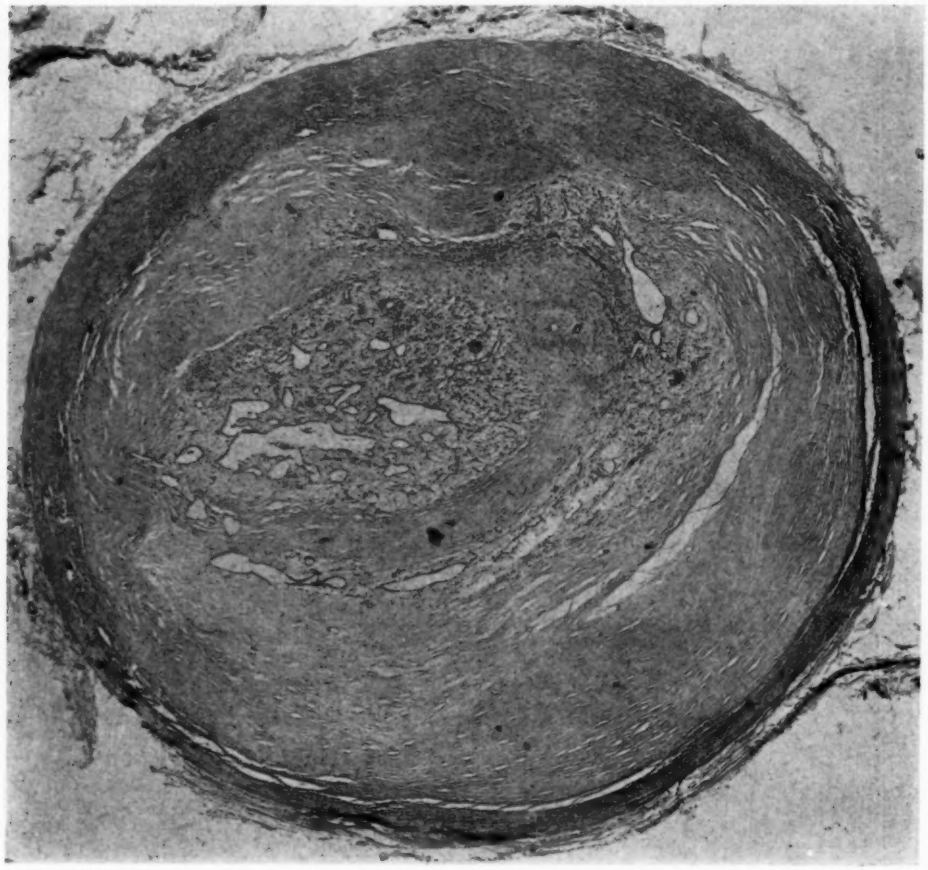

Fig. 23.—Recanalized thrombus filling lumen of sclerotic coronary artery of man 39 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 94228.

is 38. The percentage of recognized embolization, 19, is quite low. There were in the present series, however, other infarcts discovered at necropsy, especially in the lungs, kidneys, and spleen, which were either not recognized during life or which in themselves were not considered significant in the causation of death; these are not included in the 19 per cent. Bean [144] reported 34 per cent of systemic emboli in the patients in whom the thrombus was in the left ventricle.

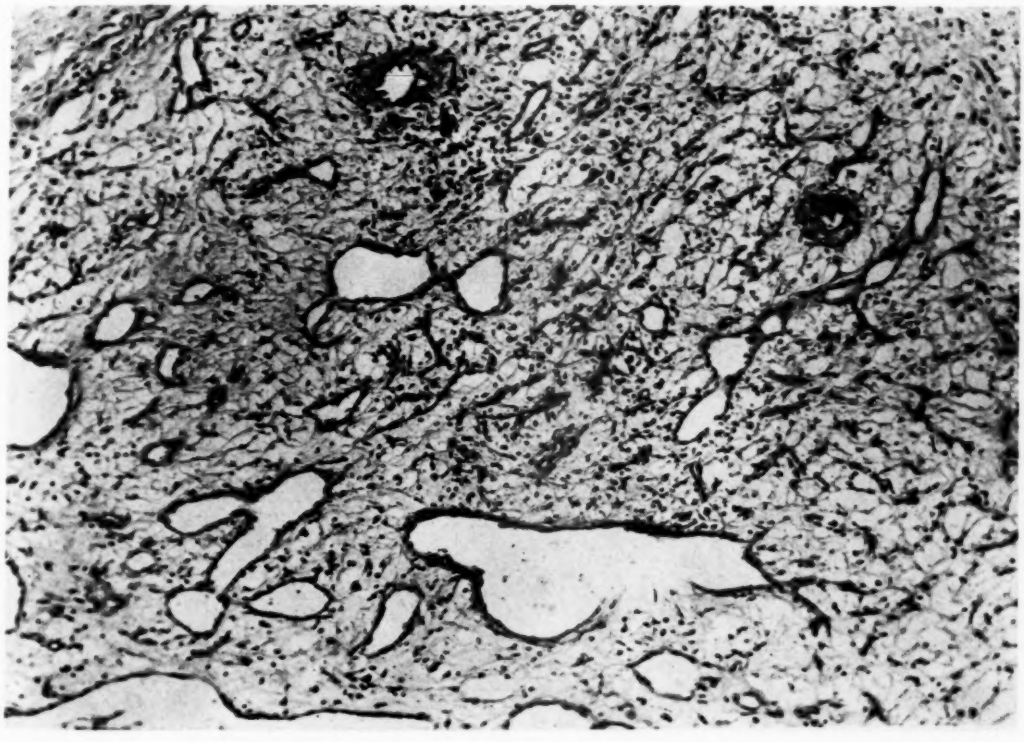

Fig. 24.—Higher magnification of recanalized thrombus of artery shown in Fig. 15, showing various sizes and shapes of endothelium-lined channels. Reduced from a magnification of × 110. A.I.P. Neg. 94227.

Valvular Abnormalities.—In ninety-three patients there were valvular lesions, eighty-two of which were plaques, nodulations, or fenestrations of no importance. The mitral valve was the site of rheumatic scarring with slight to moderate stenosis in seven patients, the aortic valve in one patient, and the mitral and aortic valves together in two patients. In one patient there was syphilitic aortitis with aortic regurgitation, as previously mentioned.

Pericardial Lesions.—The hearts of twenty-three patients presented petechiae of the visceral pericardium, ranging from few to many, more often the former. In fourteen patients with petechiae there were fresh myocardial infarcts. In one of the patients there were both fibrous and old pericardial

adhesions associated with a fresh and an old infarct. In five of the patients there was also focal fibrinous pericarditis, all with infarcts. In one patient there were old pericardial adhesions with an old infarct.

In twelve patients there was focal fibrinous pericarditis, and in all twelve of these there were fresh myocardial infarcts. In four of the twelve patients there were also pericardial petechiae. In one of the twelve patients the peri-

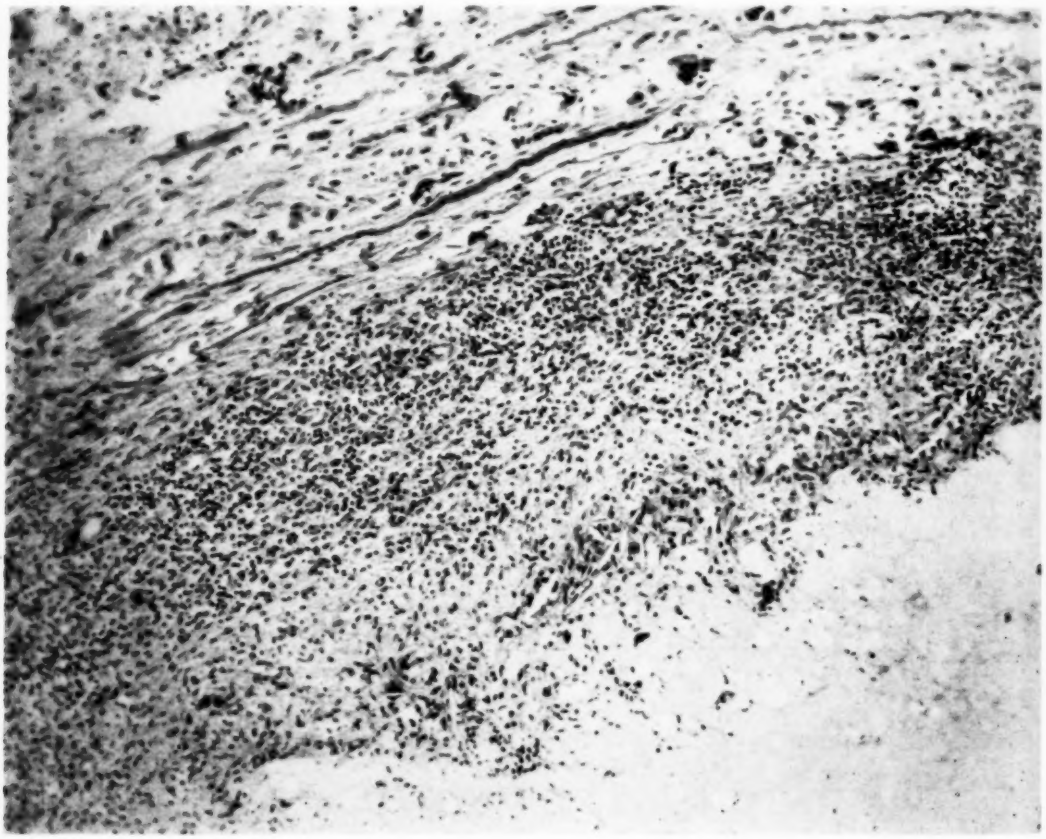

Fig. 25.—Infiltration of media of sclerotic coronary artery by mononuclear cells in a man 28 years of age. Reduced from a magnification of × 110. A.I.P. Neg. 94224.

cardium was also edematous, and in another there was 70 c.c. of a flaky, whitish exudate. In two of the twelve patients there were also patches of old fibrous adhesions. In a thirteenth patient the entire heart was encased in a fibrinous exudate ranging from 1 to 4 mm. in thickness, and there was a massive, fresh infarct of the left ventricle and interventricular septum. The incidence of acute pericarditis for the eighty-four patients with recent or organizing infarcts is, therefore, 15.5 per cent, whereas in the literature the incidence has been reported to be 28 per cent.[144]

In eight men there were patches of old fibrous adhesions; in four of these there were fresh infarcts and in two, old infarcts. Two of these patients also presented areas of fibrinous pericarditis. In a ninth patient the whole pericardial sac was obliterated by the old adhesions, and in a tenth the entire right ventricle was involved, with a calcified mass in the pericardium measuring 4 by 3 centimeters.

Fig. 26.—Fresh hemorrhage in plaque. Man 26 years of age. Reduced from a magnification of × 25. A.I.P. Neg. 94116.

Rupture of the Heart.—There were four cases of rupture of the heart with cardiac tamponade. In two patients the pericardium contained about 50 c.c. of blood, and in the other two patients, 200 cubic centimeters. In three patients the rupture was in the left ventricle and in one patient, in the right. There were fresh infarcts in three patients, in one of whom there was also an aneurysmal bulge in the left ventricle at the site of an old infarct. In the fourth patient rupture appeared to be due to puncture of the left anterior descending artery from a needle wound.

It is concluded that there were three cases of spontaneous rupture among the eighty-four patients with fresh or organizing myocardial infarcts. The incidence is 3.6 per cent, which is less than the 8 per cent incidence reported in several series of cases,[36,159,162] although there is a wide range from 0 to 20 per cent.[144]

Ventricular Aneurysm.—The hearts of four soldiers presented ventricular aneurysms, all of the left ventricle. In one of these there was a fresh infarct in the interventricular septum and petechiae of the pericardium. In another there was rupture of the aneurysm, which apparently was the result of a fresh infarct. In a third patient the aneurysm was the product of an old infarct, and in the fourth patient the cause was an old infarct which left the ventricular wall 4 mm. thick and with a calcified rim. The incidence of aneurysm on the basis of 144 cases of gross infarction in this series is 3.5 per cent, whereas the incidence in the literature varies from 5 to 38 per cent for all ages.[144]

Atherosclerosis of the Aorta.—In 191 patients (42 per cent) there was some atherosclerosis of the aorta; in 103 of these there were a few plaques, confined usually to the root of the aorta, but sometimes involving also the abdominal portion; in eighty-five others there were more numerous plaques, involving both the thoracic and abdominal portions in the majority, and in three the degree of atherosclerosis was not given. In most of these patients the amount of atherosclerosis was slight or moderate in comparison to the degree of coronary sclerosis. In a few there was severe atherosclerosis of the aorta.

Lesions in Other Arteries.—The arteries and arterioles of the various organs were examined in order to determine whether there were significant lesions. The only organs in which there were noteworthy lesions were the kidneys, the brain, and the adrenal glands. Arteriosclerosis of the kidneys was found in only six patients, arteriolosclerosis in thirty-three. The arteriosclerosis was graded 1 plus (on a basis of 4) in all but one of the six patients, in whom it was 2 plus. The arteriolosclerosis was graded 1 plus in twenty-one, 2 plus in three, and 3 plus in six patients. Arteriolar necrosis of the kidneys was noted in five patients, in whom the arteriolosclerosis was graded 1 plus.

In eighteen patients the periadrenal arterioles were hypertrophied; 1 plus in fifteen, with necrosis in three of these, 2 plus in two, and 4 plus in one. Associated renal arteriosclerosis was present in only one-half of the eighteen patients.

Cerebral arteriosclerosis in a mild to moderate degree was observed in only ten patients. In a few patients in whom there was considerable atherosclerosis of the aorta, the first portion of the intercostal arteries, lumbar arteries, celiac artery, mesenteric artery, or renal arteries was also involved.

It is apparent that coronary artery sclerosis, in this series, is a specific disease of the coronary arteries and not a part of generalized arteriosclerosis.

Renal Lesions.—There were recent infarcts in five of the kidneys and scars of old infarcts in nine. A mild degree of glomerular sclerosis was found in twelve patients.

Lesions in the Brain.—Because of the suddenness of death in this group of young soldiers, the brain was examined in 253 patients. In 181 it was found to be normal; in fifty-two there was congestion or edema; in eleven, a mild to moderate degree of arteriosclerosis; in three, an area of hemorrhage; in three, an area of softening; and in three, a subarachnoid hemorrhage of small proportion.

Congestion of Organs.—There was no congestion of the lungs, liver, or kidneys in seventy-seven patients. In sixty-four patients the lungs alone were congested, in eleven the liver alone, in twenty-eight the kidneys alone, in thirty-eight the lungs and liver, in sixty-eight the lungs and kidneys, in nineteen the liver and kidneys, and in 140 the lungs, liver, and kidneys. In eight patients the presence or absence of congestion of these organs was not remarked upon and, hence, was probably absent.

ASSOCIATED PATHOLOGIC CONDITIONS

The following lists include the lesions other than cardiovascular found among the 450 autopsied cases.

RESPIRATORY

Pleuritis or pleural adhesions	58	Pulmonary infarct	7
Pulmonary tuberculosis, healed	34	Hydrothorax	7
Pulmonary emphysema	33	Tuberculous lymphadenopathy	2
Anthracosis	18	Congenital cyst of the lung	1
Pulmonary atelectasis	13	Empyema	1
Bronchopneumonia	12	Bronchopleural fistula	1
Bronchitis	8	Pulmonary thrombosis	1
Pulmonary tuberculosis, active	7	Tracheitis	1
Pulmonary fibrosis	7		

GASTROINTESTINAL

Gastritis	12	Polyp of the colon	1
Appendicitis, acute	3	Hemangioma of the duodenum	1
Meckel's diverticulum	3	Mucocele of the appendix	1
Diverticula of the colon	2	Appendicitis, healed	1
Duodenal ulcer	2	Peritonitis	1
Diverticulum of the ileum	1	Fibrosis of the pancreas	1

LIVER, GALLBLADDER, AND BILE DUCTS

Fatty changes in the liver	40
Cavernous hemangioma	6
Portal cirrhosis	3
Cholelithiasis	2
Cholecystitis, healed	2
Cholecystitis, acute	1
Cholangeitis	1
Tuberculosis of the liver	1
Fibroadenoma of the liver	1

GENITOURINARY

Sclerosis of the kidney	23	Aplasia of the kidney	1
Renal infarct, recent and old	14	Fibroma of the kidney	1
Hyperplasia of the prostate	9	Glomerulonephritis	1
Prostatitis	9	Pyelitis	1
Double ureter	4	Fetal lobulations, both kidneys	1
Atrophy of the testis	3	Diverticulum of the urinary bladder	1
Double pelvis	2	Prostatic urethritis	1
Cyst of the kidney	2	Prostatic calculi	1
Varicocele	2	Epididymitis	1
Prostatitis, healed	2	Absent left testis	1
Seminal vesiculitis	2	Malignant tumor of the testis	1
Renal calculus	2	Fibrosis of the testis	1
Adenoma of the kidney	1	Hydrocele	1
Pyelonephritis	1	Papillomas of the penis	1

ENDOCRINE GLANDS

Hyperplasia of the thymus	5
Persistent thymus	4
Involution of the thymus	1
Adenoma of the adrenal	3
Cyst of the adrenal	3
Hyperplasia of the adrenal	2
Pheochromocytoma	1
Periadrenal hemorrhage	1
Colloid goiter	1
Adenoma of the thyroid	1
Cyst of the thyroid	1
Cicatrix of the thyroid	1
Pituitary cyst	1

SPLEEN

Splenomegaly	21
Infarct	7
Tubercles, calcified	5
Accessory spleen	4
Acute splenic tumor	3
Fibrosis	1
Granulomas	1
Sarcoidosis	1

BRAIN

Leptomeningitis	4
Infarct	3
Subarachnoid hemorrhage	3
Embolus	1
Glioma, ependymal	1
Encephalomalacia	1
Calcification of the cerebral ganglia	1

MISCELLANEOUS

Thrombophlebitis	4
Hemorrhoids	2
Lipoma of the forearm	1
Lipoma of the buttocks	1
Lipoid depletion	1
Lymphadenitis	1

PROGNOSIS

Prognosis will be discussed in a subsequent paper in which various age groups will be compared.

SUMMARY AND CONCLUSIONS

World War II has afforded an opportunity to accumulate and study 866 cases of coronary artery disease in soldiers between the ages of 18 and 39 years, inclusive, 450 of whom were examined at necropsy. Two hundred three of these 866 men were under 30 years of age. Based on this figure, which is undoubtedly too small, the death rate from this cause per 100,000 men per year was less than 0.1 in age group 18 and 19 years, 1.0 in age group 25 to 29 years, 3.4 in age group 30 to 34 years, and 12.7 in age group 35 to 39 years. Therefore, deaths from coronary artery disease were more than thirty times as common in men 35 to 39 years of age as in those 20 to 24 years of age.

If these are assumed to be the rates for the entire population of the United States, it means that each year coronary artery disease will be the cause of death for twenty-four men 20 to 24 years of age, for fifty-four men 25 to 29 years age, for 183 men 30 to 34 years of age, and for 637 men 35 to 39 years of age. These figures are based on the estimated population of the United States for 1944 and 1945 published by the Bureau of the Census, Jan. 27, 1946.

There are sixty-three Negroes in the series. Since 10 per cent of the men in the entire Army were Negroes, this figure indicates that the rate of incidence of coronary artery disease among Negroes was approximately two-thirds that among Caucasians.

A study was made, both by means of questionnaires sent to the nearest of kin of the dead men and from histories obtained directly from those who survived, of many etiological factors, and these data were compared with similar information gathered from control groups. The only important conclusion that could be drawn concerned the effect of heredity, there being four times as many cases of cardiovascular disease in the immediate families of the survivors as in those of the control group.

Since many of the men appeared to be overweight at the time of death or of acute myocardial infarction, the factor of obesity was investigated. It was found that on induction the weight of these men corresponded to the average weight of all inductees and that during their Army careers they gained weight almost in the same relative degree as other soldiers. The weight gain of those who died paralleled that of the average soldier more closely than that of the survivors,

in whom there was a slight tendency to be overweight. Therefore, it appears that obesity cannot be said to be an etiological factor of any importance.

There was a slight though definite disposition toward hypertension in the group regarding both systolic and diastolic pressures, but more particularly the latter, and more notable in the survivors than in the men who died. However, only twenty-four men were considered clinically to be truly hypertensive. Nevertheless, in 27.9 per cent of the series systolic pressures were above 139 mm. Hg as compared with 8.9 per cent for an amputee control group, and in 19.1 per cent of the series diastolic pressures were above 89 mm. Hg as compared with 3.8 per cent for the control group.

The men in this series generally served for much shorter times than the men in the Army as a whole, which indicates that the rigors of Army life may have played a role in precipitating death. Death occurred in 45 per cent of the fatal cases during the first year of service and acute myocardial infarction in 34 per cent of the survivors within that period. There was a definite tendency for the older men to die earlier in their army careers.

The time of year and geographic location had no apparent influence in precipitating death.

The onset of the terminal illness or the "coronary attack" occurred relatively more often during strenuous activity than during mild and moderate activity and sleep. The proportion of attacks occurring during strenuous activity was more than twice as great as the proportion of the time spent in such activity, the proportion during mild and moderate activity was about equal to the proportion of time thus spent, and the proportion of men stricken while asleep was about one-third that of the proportion of time normally spent in sleep. The percentage of patients with an old or organizing thrombus in a coronary artery was considerably less among those who died while asleep than among those who died while engaged in waking activities. Conversely, the percentage of those with fresh thrombi was greater among the men who died in their sleep than in those who experienced the "attack" during activity.

Many men had had previous symptoms of cardiac disease, 9.3 per cent within three weeks of the "attack" ("premonitory" symptoms), 31.5 per cent with definite symptoms three weeks or more before the "attack," and 8.6 per cent with probable or possible symptoms of cardiac origin more than three weeks before the "attack." Therefore, about one-half of the men had symptoms before the onset of the "attack." Of the 450 men who died, fifty-seven had had anginoid attacks three weeks or more before death. These were mainly more or less isolated attacks of "coronary insufficiency" with pain, weakness, sweating, and sometimes dyspnea and other symptoms. Eight other men had had symptoms of partial or complete congestive failure. Seventy-three of the 400 survivors had had angina of effort, and in sixty-four other patients, there were attacks suggestive of "coronary insufficiency" and even coronary thrombosis, some with dypsnea as the main symptom. Twenty-eight of the men who died had had attacks that were suggestive but not typical of coronary insufficiency, most of them with symptoms referred to the abdomen. Twenty-seven of the survivors had had symptoms of similar nature, but dyspnea on exertion was noted more often than

abdominal complaints. The "prodromal symptoms" that were present in sixty men within three weeks of the "attack" were, in general, similar to the attacks that occurred in other men three weeks or more before the "attack." Several men had been hospitalized previously for cardiac complaints. The diagnosis of cardiac disease was made in some of these but not in others.

There was no correlation between the presence or absence of a previous cardiac history and the pathologic changes found, although men with previous cardiac symptoms tended to have myocardial infarcts or myocardial scars more frequently.

Of the 450 patients who died, death occurred within twenty-four hours of the onset of symptoms in 375 (83.3 per cent). Age did not appear to be related to the duration of the terminal illness. Duration of illness, on the whole, was also not related to the lesion found. However, the longer a man lived the more likely he was to have myocardial infarction whether or not he had a previous cardiac history.

Pain was present in 98.4 per cent of the men, being the primary or first symptom in 575, but ensuing rapidly in the other fifty-seven of the 642 patients in whom a history could be elicited. Manifestations of shock were the next most common symptom at the onset, occurring in 17 per cent, but nearly eight times more often among the men who died than among those who lived. Dyspnea occurred soon after the onset in 58 per cent, nausea, vomiting, or both in 36 per cent, and nervous manifestations in 18.5 per cent. Unconsciousness occurred in 11 per cent, indigestion in 7 per cent, dizziness in 6 per cent, and convulsions in 4 per cent. Diarrhea developed during the "attack" in fourteen patients. Several symptoms occurred almost simultaneously from the start in many instances. Congestive failure occurred during the "attack" in ten men, and hemiplegia, in five.

In general, the pain was similar to that well known for coronary artery disease. Radiation occurred from the primary site in nearly 67 per cent of the cases. A feature of great interest was exacerbation of the pain on deep inspiration in 10 per cent of the survivors. None of these men had pericardial or pleural friction rubs.

Of the fifty-four men who died during hospitalization, thirteen developed congestive failure, embolization occurred in five, and convulsions occurred in six. Pain recurred in forty-five of these men and was present terminally in twenty-two.

Of the 400 survivors, cardiac enlargement was thought to be present in sixteen. Poor heart sounds were noted in seventy-two men. Premature ventricular contractions occurred in fifty-seven patients, paroxysmal auricular tachycardia in two, auricular fibrillation in two, and auricular flutter in one. These arrhythmias were all transient. Systolic murmurs were heard in thirty-three men and diastolic murmurs, in two. These also were transient. Gallop rhythm was noted in twenty patients and it persisted in three. Signs of pulmonary congestion occurred in forty-one patients during the "attack." Transient pericardial friction rub was heard in twenty-eight patients.

The behavior of the blood pressure among the survivors during the attack was interesting. In practically 20 per cent of the men there was a rise in both systolic and diastolic pressures in the initial stage of the "attack." Both systolic and diastolic pressures dropped in only 14 per cent of the cases. In 70 per cent of the patients the blood pressure remained normal or returned to normal within twenty-four hours after the initial period of hospitalization and continued to be normal throughout the period of observation in the hospital. In the 22 per cent of the patients in whom there was either an elevation or lowering of the pressures during the acute "attack," normal levels were reached forty-eight hours or more after the onset of the "attack." In 4 per cent of the patients the pressure was constantly elevated during convalescence, and in 4 per cent it was constantly low during convalescence.

The electrocardiograms made in some of the men who died showed some discrepancies with the lesions found, but in general, they agreed. Serial electrocardiograms were made in all who survived. Anterior infarction was indicated in 176 patients, posterior infarction in 113, some form of lateral infarction in 56 patients; nonlocalizing electrocardiographic changes were present in fifty-five.

Among 274 patients with adequate data, elevation of temperature, leucocytosis, and increased sedimentation rate occurred in 58 per cent; two of these three abnormalities were present in 28 per cent; and one abnormality existed in 12 per cent. In only 2 per cent were the temperature, white blood cell count, and sedimentation rate normal. In general, there was parallelism of the three findings.

The clinical course of the survivors showed asymptomatic recovery in 57 per cent, recurrence of pain in 25 per cent, congestive failure in 2 per cent, pulmonary congestion in 4 per cent, dyspnea without râles in 5 per cent, pulmonary infarction in more than 1 per cent, and pleural effusion in almost 1 per cent.

Diagnostic accuracy was 58 per cent in the men who died and 71 per cent on first examination in the survivors.

Seventeen of the 400 have survived another acute myocardial infarction and twenty-eight have developed congestive failure. Dyspnea on exertion has been the most prominent symptom following healing of the infarct, with angina of effort running a close second (62 and 52 per cent respectively). Tiredness has been fairly common. Fifty per cent of 361 men adequately followed up have returned to full-time employment; 41 per cent have not been able to work at all.

The Negroes were studied separately and were found to present clinical and pathologic features in every way similar to the Caucasians.

All of the 450 hearts examined at necropsy had advanced arteriosclerosis of the coronary arteries. There were 114 with gross myocardial infarction, fourteen with two infarcts, and two with three infarcts. In eight hearts no complete occlusion of any artery was found; in twenty-seven hearts there was sclerotic occlusion alone, in fifty-five, thrombotic occlusion alone, and in twenty-four, both sclerotic and thrombotic occlusion. Of the 336 patients without gross myocardial infarction, there were thirty-eight without complete occlusion of any artery, 148 with sclerotic occlusion alone, 117 with thrombotic occlusion alone, and thirty-three with both sclerotic and thrombotic occlusion.

The lesions of the coronary arteries were similar to those of the coronary arteries in cases of coronary artery sclerosis in patients over 40 years of age, but they were found to be more advanced in age as the men advanced in years. The atheromatous plaque was the prominent lesion of the arteries microscopically. Hemorrhage in the plaque was found in 12 per cent.

Fifty-two per cent of the hearts were hypertrophied, 16 per cent moderately or greatly so. There were no more than sixteen patients with hypertension at the time of the fatal "attack" and only six patients with valvular disease in whom the hypertrophy could be accounted for on any other basis than the effects of coronary artery disease. Myocardial infarction and myocardial scars were the most prominent factors associated with hypertrophy, in addition to the coronary arteriosclerosis. Men with the larger hearts tended to live longer.

Cardiac dilatation of moderate degree was found in twenty-four patients and of severe degree in six patients.

The myocardial infarcts, numbering 130 found on gross examination and twenty-three on microscopic study, were located in the left ventricle and/or interventricular septum in all but seven patients, in whom they were in the posterior wall of the right ventricle. They were in the posterior wall of the left ventricle in twelve patients and in the lateral wall of that ventricle in five patients. The gross infarcts were fresh in sixty-eight patients, organizing in twenty-two, old in thirty-four, and of unstated age in six. In sixteen patients there were two gross infarcts. They varied in size from microscopic to more than 6 cm. in diameter.

Scars were present in the myocardium in 262 patients.

In forty-six patients the coronary arteries were sclerotic but their lumina were not occluded. In 232 men there was practically complete sclerotic occlusion in some part or parts of one or more coronary arteries; in 192, in the left anterior descending branch, in fifty-nine, in the right coronary artery, and in sixty, in the left circumflex branch. Sclerotic occlusion was present in two or all three of the arteries in sixty patients. In 229 patients there was thrombotic occlusion, recent, organizing, or old, in some part or parts of one or more coronary arteries; in the left anterior descending branch in 174, in the right coronary artery in forty-nine, in the left circumflex in twenty-eight, and in two or all three of the arteries in nineteen patients. The great majority of the occlusions were in the proximal one-third of the arteries. There were fresh thrombi in 156 men, organizing thrombi in nineteen, old thrombi in twenty, both old and fresh thrombi in twelve, and thrombi of unstated age in twenty-two patients.

Mural thrombi were present in forty-three patients (38 per cent of the 144 with gross myocardial infarcts).

Rheumatic valvular disease was present in ten patients and syphilitic aortitis in one patient.

In twelve patients there was focal fibrinous pericarditis and in one patient, diffuse fibrinous pericarditis. Patches of old fibrous pericarditis were found in nine patients and old total obliterative pericarditis in one patient.

There were four examples of rupture of the heart with cardiac tamponade. One of these may have been the result of puncture of a coronary artery by a

needle inserted for the purpose of resuscitation. Ventricular aneurysm was found in four patients.

In 191 patients there was atherosclerosis of the aorta, but in 103 the lesions were comparatively insignificant. Important sclerosis of other arteries was numerically insignificant.

There was some congestion of the lungs, liver, and/or kidneys in all but seventy-seven patients.

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A CLINICAL EVALUATION OF VERATRUM VIRIDE IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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AS A therapeutic agent veratrum viride fell into disrepute many years ago. Formerly it was used to "soften the pulse" and lower the body temperature in infectious fevers. These effects were produced by administration of the drug in doses sufficient to cause collapse.[1] The tinctures in use at that time were so poorly standardized that the effective dose could not be calculated in advance. Because it slowed the pulse and lowered the blood pressure, often to a state of collapse, veratrum was thought to be a "cardiac depressant." For these various reasons the drug has been condemned in textbooks of pharmacology.[1-3] Actually, however, veratrum viride was cast into discard[3] before its pharmacologic effects on the circulatory system had been elucidated.[4]

A review of the more recent pharmacologic data concerning the veratrum alkaloids indicates that a significant reduction in arterial pressure occurs with doses below the toxic level.[5] The fall in arterial pressure apparently is associated with peripheral vasodilatation rather than with depression in cardiac output.[5,6]

Much pharmacologic evidence has accumulated to show that the circulatory effects of veratrum are mediated through nervous pathways. The reduction in blood pressure and cardiac rate observed with subtoxic doses in animals may be abolished by section or cold block of the vagus nerves.[5] Amann and Schaefer[7] have recently demonstrated that various afferent fibers are present in the cardiac branches of the vagus nerves which carry bursts of electrical activity in phase with the heart beat. These afferent nerves can be caused to fire off continuously by the injection of veratrine. Dawes[8] has confirmed in dogs and cats the fact that the reflex fall in blood pressure and heart rate following the injection of veratridine originates from the afferent vagus nerve endings in the myocardium of the left ventricle and in the lungs. This interesting laboratory evidence suggests that there is a vasodepressor mechanism mediated through the afferent vagus nerve endings in the thorax which can be excited to continuous activity by the veratrum alkaloids.

The effects of veratrum in the treatment of essential hypertension have not been extensively studied. Collins[9] observed the results of a single dose of

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the tincture in hypertensive patients. He concluded that definite and often striking reductions in blood pressure could occur with the use of subtoxic doses, but he made no attempt to treat his patients over long periods of time. The hypotensive effects were confirmed by Wedd[10] and by Hewlett and associates.[11] Hite[12] treated hypertensive patients continuously for eight months and concluded that veratrum viride is a valuable therapeutic agent in this disease. The drug has been used for many years in the treatment of eclampsia.[13-15] However, the available pharmacologic and clinical data suggested to us the need for re-evaluation of veratrum viride with particular reference to its use as a therapeutic agent in the treatment of essential hypertension. This communication reports the results of a clinical trial of this drug in a series of forty hypertensive patients. Experimental studies of the hemodynamic effects of veratrum, especially upon cardiac output, peripheral resistance, hepatic blood flow, renal clearances, sympathetic reflexes, limb and digit plethysmography, and skin temperatures will be reported elsewhere.[6]

SUBJECTS AND METHODS

The subjects were a heterogeneous group of forty patients with essential hypertension who were treated on the wards and in the Outpatient Department of the Massachusetts Memorial Hospitals. The period of observation under veratrum treatment varied from several weeks to as long as thirteen months. Thirty-one of the patients received the drug for periods longer than two months. Prior to treatment all patients were observed under routine symptomatic therapy including rest, sedation, and the usual forms of psychotherapy. Nine patients had previously received treatment with potassium thiocyanate and eight had received pentaquine.[16] Fifteen of the patients received treatment with a salt-free diet or the "rice diet." In all except the special instances described below, previous dietotherapy and drug therapy were withdrawn before veratrum was administered.

The blood pressure was measured with a mercury manometer with the patient in both the erect and the supine positions after he had rested for at least fifteen minutes in the supine position. The pulse rate was counted at the wrist or the cardiac apex.

The veratrum preparation used was the whole powdered mixture of alkaloids prepared in tablets. This preparation, which in our experience has had a fairly uniform potency, was biologically standardized so that each tablet contained 10 "Craw units."*

RESULTS

Therapeutic and Toxic Dosage.—The therapeutic dose of veratrum viride varied from 10 to 40 Craw units in those patients who responded to the drug. Increasing the dosage beyond this point resulted in further reduction of blood pressure, but inevitably led to toxic reactions. The margin between the therapeutic

*The preparation of veratrum viride which bears the trade name of "Vertavis" was generously supplied by Irwin, Neisler, and Co., Decatur, Ill. A Craw unit is defined as the amount which causes cardiac arrest in the crustacean, *Daphnia magna*.

and toxic doses usually was no greater than 10 Craw units. For any given individual the effective dose could be determined only by trial with gradually increasing doses. The therapeutic dose bore no relation to the surface area of the patient or the severity and duration of the disease.

If the effective dose was greater than 10 Craw units, ingestion of the total dose at one time frequently resulted in side reactions, particularly nausea and vomiting. However, by subdividing the total effective dose so that no more than 10 Craw units were administered at hourly intervals, these side reactions were reduced considerably.

Time-Dose Relationships.—Although there was great individual variation in the size of the effective dose (herein defined as that dose which resulted in a reduction of at least 20 mm. in systolic and 15 mm. in diastolic blood pressure), the onset and duration of the hypotensive response was quite uniform in different patients. When an effective dose was administered, the hypotensive response began in one or two hours, reached a maximum in four to six hours, and ended in approximately twelve to fourteen hours. An example of this sequence is provided by a patient admitted to the hospital because of hypertensive crisis with encephalopathy.

CASE 1.—J. Mc., a 51-year-old white man, was admitted to the Evans Memorial Hospital on June 16, 1947. On the day of admission he was seen in the outpatient department where he was found to be mentally confused. The blood pressure, which had previously been 240/130, had risen to 270/170. In the hospital he was observed to be disoriented as to time and place; he exhibited echolalia, mixed visual and verbal agnosia, and acoustic agnosia. Neurological examination revealed no localizing signs. Venesection was performed with the removal of 500 ml. of blood without significant reduction of blood pressure.

Veratrum viride was then administered in amounts of 10 Craw units every hour for three doses followed by 10 Craw units every other hour for three doses (Fig. 1). Eight hours after veratrum was begun, the blood pressure had fallen to 150/60, and the pulse rate, from 125 to 80 per minute. Eight hours after veratrum had been discontinued, the blood pressure began to rise again, stabilizing at 230/140 sixteen hours after the last dose of the drug. The pulse rate rose to 100 per minute. During the period of hypotension there was gradual clearing of the sensorium so that twenty-four hours after admission the patient was oriented as to time and place and was able to carry on an intelligent conversation.

If the dosage intervals were not separated by at least eight hours, successive doses soon resulted in the appearance of toxic reactions. The toxic effects resulting from cumulative overdosage may be illustrated by the following case.

CASE 2.—L. S., a 39-year-old white woman, with known hypertension for eight years, complained of dyspnea, orthopnea, and dependent edema for five months prior to admission to the hospital. After two weeks of hospital treatment with digitalis and mercurial diuretics, the signs of cardiac failure cleared. The blood pressure at this time was 210/135. Treatment with veratrum was begun and the dosage was gradually increased to 90 Craw units per day administered in divided doses of 30 Craw units at 10:00 A.M., 2:00 P.M., and 6:00 P.M. At 6:30 P.M. the patient experienced numbness in the feet, hands, and lips, blurred vision, increased sweating, soon followed by nausea with severe vomiting, excess salivation, and collapse in the upright position. The blood pressure at this time was 120/80 and the pulse rate, 54 (Fig. 2). These symptoms gradually abated during the next three hours and had completely disappeared in sixteen hours.

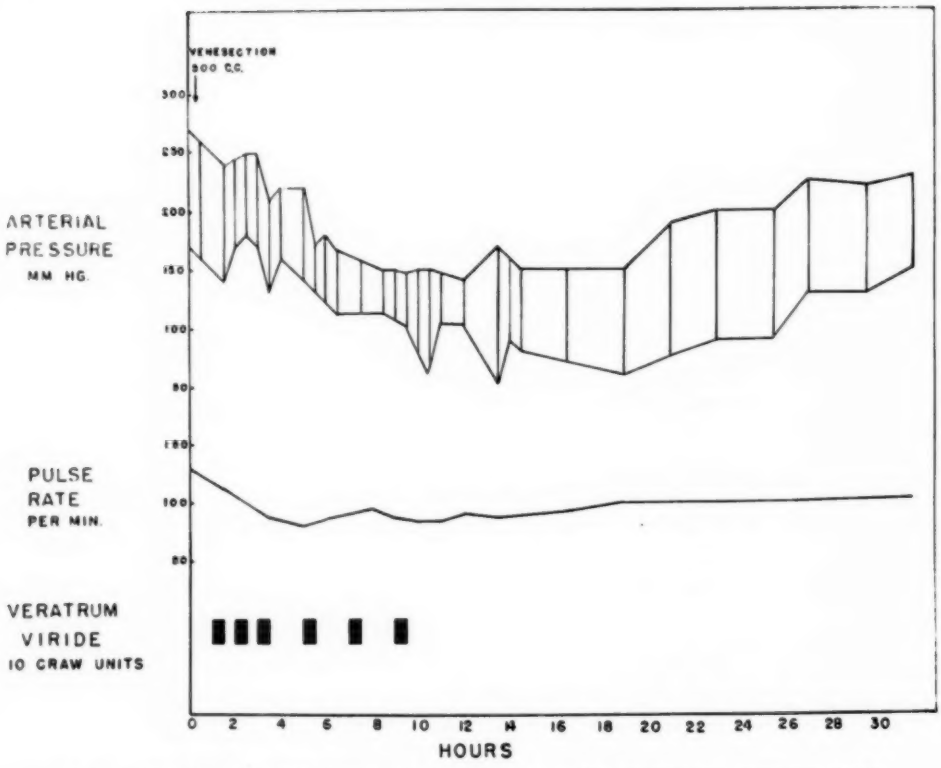

Fig. 1.—The duration of the hypotensive response to orally administered veratrum viride as shown in Patient J. Mc. (Case 1).

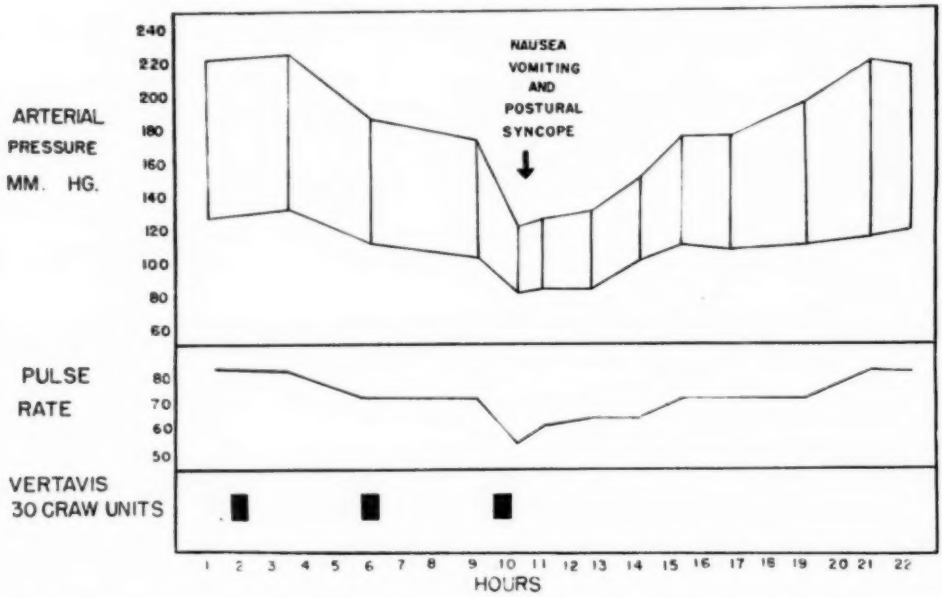

Fig. 2.—The toxic reaction resulting from the effects of cumulative overdosage when veratrum was administered at intervals of four hours (Case 2).

This patient received three doses of 30 Craw units at four-hour intervals. Since veratrum is present and active in the body for twelve hours, at 6:30 P. M. she suffered the toxic reactions resulting from a cumulative dose of 90 Craw units. Such severe reactions were fairly frequent in the early phase of the investigation, but were almost completely eliminated when the effective doses were separated by a twelve-hour interval.

Therapeutic Results.—

Hospitalized Cases: In order to evaluate the hypotensive activity of veratrum viride under controlled conditions, the drug was administered to six hospitalized patients who had shown little hypotensive response to other types of medical treatment, including hospital bed rest (Table I). During the control period three patients received sedation in the form of phenobarbital (30 mg. three times per day), two patients received the Kempner rice diet[17] for ten days and two weeks, respectively, and one patient was given a "salt-free" diet supplemented with mercupurin (2.0 c.c. intravenously twice per week). The period of control observations in the hospital varied from ten to thirty days prior to the institution of veratrum treatment.

In each case all blood pressures were recorded by the same individual. The blood pressure taken initially was not recorded and the patient was then allowed to rest for thirty minutes. Following this initial period, the blood pressure and pulse rate were recorded once a minute for five minutes in the supine position, followed immediately by five minutes in the erect position, and then a final five minutes in the supine position. In the control period the lowest values for systolic pressure, diastolic pressure, and pulse rate were selected to compare with the highest values recorded in the period after treatment with veratrum viride.

Although all of these patients were hospitalized throughout the study, they were not in bed at all times, except four patients whose blood pressures were recorded after forty-eight hours or more of complete rest in bed. In every case, after treatment with veratrum was begun, patients were allowed to be up and about the ward. The previous regimen of treatment was continued, the only change being the addition of veratrum viride.

The results listed in Table I indicate that in five of the six cases a significant reduction in blood pressure occurred following therapeutic doses of veratrum viride. In one case (Patient L. S.) significant hypotension did not occur after therapeutic doses, but developed only after toxic doses. In the four cases in which the drug was withdrawn, there was a prompt return of blood pressure to pretreatment levels.

Outpatient Cases: The foregoing results seemed sufficiently significant to warrant further clinical trial of veratrum viride over longer periods of time in ambulatory patients. The latter data are summarized in Table II. Of the thirty-four patients studied, all except four exhibited a significant reduction in blood pressure when compared with the values obtained during the control period. However, the results were seldom as striking as after acute administration of the drug in the hospital, and in only one case did the blood pressure fall to normal.

TABLE I. THE HYPOTENSIVE EFFECT OF VERATRUM VIRIDE COMPARED WITH THAT OF OTHER FORMS OF THERAPY IN HOSPITALIZED PATIENTS

PATIENT	SEX	AGE (YEARS)	KNOWN DURATION OF HYPERTENSION (YEARS)	TIME AFTER ADMISSION TO HOSPITAL (DAYS)	TREATMENT	BLOOD PRESSURE		PULSE RATE PER MINUTE
						LYING	STANDING	
C. S.	M	43	10	1	0	234/160	253/172	90
				3	Complete bed rest 48 hrs.	232/146	233/160	85
				10	0	225/130	210/150	92
				12	Vertavis, 30 Craw units b.i.d.	190/110	190/130	68
				15	Vertavis discontinued	225/130	222/154	84
R. Mc.	M	38	1	1	0	190/140	185/140	72
				14	Low-salt diet; mercurials	170/135	170/140	68
				16	Vertavis, 10 Craw units daily	142/100	120/90	58
M. S.	F	48	6	1	0	218/140	215/152	75
				3	Complete bed rest 48 hrs.	210/130	220/145	75
				30	Strict rice diet 10 days	190/130	190/150	82
				34	Vertavis, 40 Craw units, single dose	155/105	160/130	90
				43	Vertavis discontinued	220/138	215/144	82
				48	Vertavis, 30 Craw units b.i.d.	175/115	180/125	80

L. S.	F	43	8	1	0	218/160	225/160	115
				14	Phenobarbital, 30 mg. t.i.d.	215/120	210/140	80
				18	Vertavis, 90 Craw units (over 8-hr. period)	150/80*		64
				20	0	220/120	210/135	82
				21	Vertavis, 40 Craw units b.i.d.	200/120	200/120	84
C. B.	M	43	2	1	0	220/140	240/160	85
				3	Complete bed rest 48 hrs.	232/145	222/158	82
				10	Phenobarbital, 30 mg. t.i.d.	240/140	230/155	80
				14	Vertavis, 30 Craw units b.i.d.	195/130	160/130	60
				24	Vertavis discontinued	220/130	230/150	82
P. P.	M	41	5	1	0	240/145	235/160	70
				4	Complete bed rest 72 hrs.	235/140	215/160	65
				18	Strict rice diet 2 weeks	240/162	208/170	76
				23	Vertavis, 30 Craw units b.i.d.	180/135	146/126	62
				27	Vertavis discontinued 24 hrs.	230/138	220/155	74
				33	Vertavis, 30 Craw units b.i.d.	146/96	130/104	50

*Collapse, nausea, and vomiting.

Except for the periods of complete bed rest noted, the patients were up and about the ward. Prior to veratrum, different types of medical therapy were substituted as indicated. When treatment with veratrum was started, the immediately preceding medical therapy was continued and was maintained even after veratrum was discontinued.

TABLE II. RESULTS OF THERAPY WITH VERATRUM VIRIDE IN THIRTY-FOUR AMBULATORY HYPERTENSIVE PATIENTS TREATED FOR PERIODS OF 1 TO 13 MONTHS

PATIENT	SEX	AGE	KNOWN DURATION OF HYPERTENSION (YEARS)	CONTROL PERIOD						AFTER VERATRUM VIRIDE						
				DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	CRAW UNITS PER DAY	DURATION OF OBSERVATION (MONTHS)	NUMBER OF VISITS	MEAN OF BLOOD PRESSURE RECORDINGS—MM. HG		MEAN PULSE RATE SUPINE PER MINUTE	TOXIC REACTIONS	SYMPTOMATIC IMPROVEMENT
						SUPINE	ERECT					SUPINE	ERECT			
C. B.	F	52	10	2 weeks*	14	235/140	220/140	76	50	13	46	200/125	165/110	78	0	++
R. Mc.	M	38	1	2 weeks*	28	170/140	170/140	60	30	10	12	160/100	150/110	54	0	+++
C. S.	M	45	8	2 weeks*	14	225/140	225/145	80	60	12	14	210/125	205/125	68	+	+++
G. P.	M	48	7	12	6	190/120	190/125	95	50	13	18	170/110	155/110	68	0	++
P. E.	F	44	13	1	3	220/135	200/140	80	60	4	9	170/100	145/110	76	+	+++
J. F.	M	56	2	1	3	240/100	210/105	82	80	6	8	200/85	170/95	64	+	0
V. F.	F	36	13	8	6	255/150	265/170	108	80	2	5	245/160	245/160	103	0	+
C. F.	M	52	1	4	7	210/120	210/120	76	60	9	20	180/105	170/110	76	0	++
R. K.	M	52	10	1	3	200/115	210/135	72	30	2	4	180/100	160/100	68	0	0
J. Mc.	M	66	6	2	4	240/145	235/150	104	50	6	9	210/130	190/130	90	0	+++
I. S.	M	46	6	2 weeks*	60	170/110	180/130	84	70	2	4	150/110	150/120	76	0	+
E. S.	F	50	21	2	4	240/140	195/150	84	70	6	14	210/120	180/120	72	+	+
E. A.	F	54	4	3 days*	10	240/150	220/160	100	50	10	12	225/130	210/140	90	0	++
N. F.	M	34	0	6	5	170/125	155/125	72	40	2	4	150/100	140/110	65	+	+

F. G.	F	45	28	3	4	255/120		78	30	6	8	240/115		70	0	+++
P. H.	F	47	0.2	1	4	230/130	180/130	76	30	3	4	180/100	160/110	0	+	++
J. C.	M	51	0.3	10	20	210/145	180/140	68	40	2	6	195/125	160/115	68	+	+
J. D.	M	38	7	2	4	180/120	160/130	88	40	2	5	160/105	160/105	82	0	0
E. S.	F	45	0	1 week*	24	225/140	190/130	90	60	2	4	185/120	170/115	54	0	+++
I. P.	M	30	6	3	4	160/120	170/130	80	50	3	3	145/95	135/110	76	0	+
J. S.	M	57	6	7	4	170/90	160/90	74	40	1	3	135/75	145/85	70	0	0
A. C.	M	45	0.5	6	8	180/110	170/100		70	1	3	145/90	140/90	72	0	+++
M. C.	F	42	6	8	5	185/120		84	20	4	5	160/90		84	0	+++
C. D.	F	43	1	6	10	215/130	195/125	92	50	2	6	185/120	170/125	94	0	++
W. G.	M	49	2	1	4	190/130	190/140	100	50	4	4	170/110	180/130	80	0	+++
M. A.	M	41	7	1 week*	7	170/115	165/120	110	50	10	12	170/120	170/120	94	0	++
L. Mc.	F	51	12	12	6	215/110	210/120	65	30	3	8	165/95	150/100	58	+	0
F. D.	M	30	0.6	4 weeks*	28	180/120		76	60	2	10	130/85	125/90	70	+	+
M. A.	M	41	7	5	8	210/130	200/140	80	60	4	6	190/130	170/120	80	+	+
N. C.	M	54	0.4	3	6	190/110	180/120	90	40	4	8	190/110	140/100	68	+	+++
L. B.	F	46	5	1	4	190/115	210/120	80	60	3	10	185/120	165/115	72	+	+
E. H.	F	57	0.5	2	4	190/115	180/120	112	50	1	4	165/105	133/110	120	0	++
W. B.	M	46	0.5	1	3	200/115	190/120	80	30	1	2	155/105	160/110	76	0	+
M. D.	M	43	2	3	5	180/120	175/125	76	50	2	4	150/95	155/105	64	+	+

*Observations made in the hospital.

Twenty-seven of the thirty-four patients (79 per cent) expressed subjective improvement. Three patients felt worse while taking the drug, and the remaining four patients either had no complaints prior to or during treatment or noted no change in their symptoms. The most remarkable improvement occurred in those patients who complained of exertional dyspnea and palpitation. Many patients noted a general improvement in physical and mental well-being which often was associated with a definite hypotensive response.

In several of the patients who had been taking veratrum for periods longer than one month, reductions in the cardiac silhouette by roentgenography as well as changes toward normal in the electrocardiogram were demonstrated (Figs. 3 and 5). There was no evidence of change in renal function as measured by concentration tests, routine urinalysis, and the excretion of phenolsulfonphthalein.

Following treatment with veratrum viride, a remarkable dilatation of the retinal arterioles has been reported in a patient with eclampsia.[18] A similar relaxation of arteriolar spasm was occasionally observed in the optic fundi in this series of patients with essential hypertension. In one patient, in whom there was generalized constriction of all the branches of the ophthalmic artery with numerous local spasms in the nasal branches, the caliber of the vessels reverted entirely to normal during the period of hypotension. Such marked changes were seen only in those patients who exhibited great reductions in blood pressure.

The most interesting results with veratrum were obtained in the so-called "resistant" types of cases. Patients with high diastolic and/or wide pulse pressure, those with long-standing hypertension, and those with cardiac failure or repeated cerebrovascular accidents responded as well as the early mild cases. Sex and age did not materially alter the response to the drug. A number of the patients in this series, although far from cured, were able to return to work from a life of semi-invalidism. The following cases serve as illustrative examples:

CASE 3.—C. S., a 45-year-old white man, had a history of two cerebrovascular accidents in the fifteen months prior to admission to the hospital. On the advice of his physician he retired from his work as manager of a bakery. In the hospital he was found to have cardiac enlargement, Grade III arteriosclerotic and Grade II hypertensive changes in the eye grounds, and impaired renal function without nitrogen retention. After two weeks of rest in the hospital, during which time he received a salt-free diet, the blood pressure was 240/130.

Treatment was begun with veratrum and the dosage was increased to 30 Craw units every twelve hours. The blood pressure fell immediately to 190/110. He was discharged from the hospital feeling considerably improved and within a month had returned to work. During the past eight months his blood pressure was never higher than 210/120 on repeated outpatient visits and usually was well below this figure.

He was readmitted to the hospital for further study seven months after beginning treatment with veratrum. Re-examination of the heart by roentgenography revealed diminution in cardiac size. The electrocardiogram showed changes toward normal since the examination seven months previously (Fig. 3).

After the second hospital day the medication was discontinued for fifty-four hours. It will be noted in Fig. 4 that soon after the medication was withdrawn the blood pressure gradually rose from a general level of 185/110 to a level of 230/120. With the resuming of veratrum therapy the blood pressure returned to the lower level. It is of interest that when the drug was discontinued the patient complained of headache and palpitation which again disappeared after treatment was resumed.

The following case demonstrates the effect of veratrum in a patient with cardiac failure secondary to hypertension.

CASE 4.—R. Mc., a 38-year-old resort hotel manager, noted the onset of exertional dyspnea, substernal oppression, and occasional attacks of paroxysmal nocturnal dyspnea eight months prior to admission to the hospital. Five months before admission he consulted his physician who found his blood pressure to be 220/140. He was advised to stop work and was given digitoxin, 0.2 mg. per day, nitroglycerin, and occasional injections of mercurial diuretics. He failed to improve, however, and was admitted to the hospital.

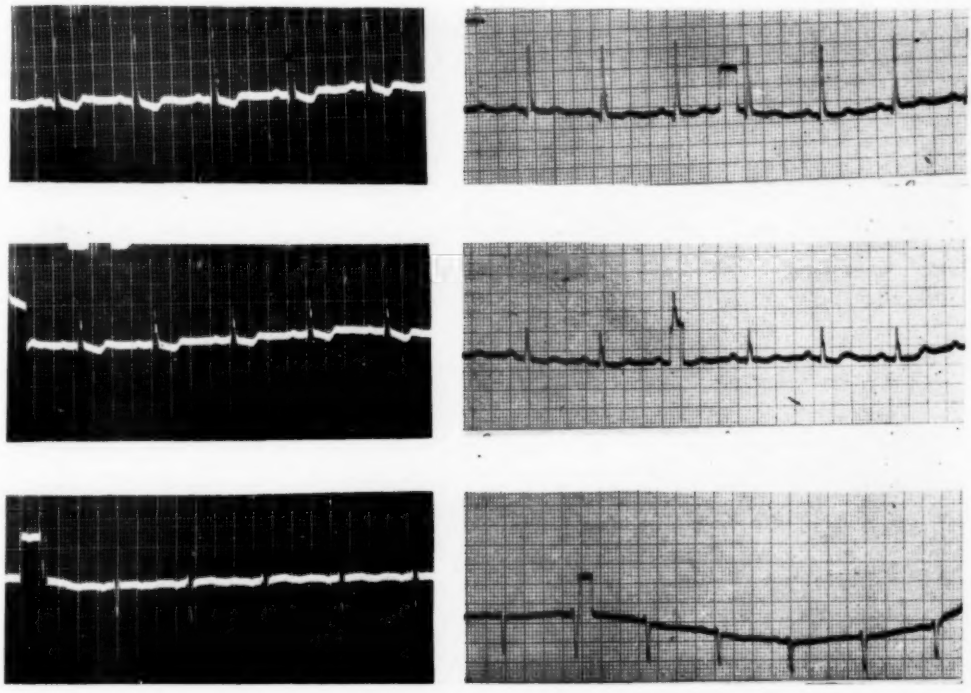

Fig. 3.—Electrocardiograms of Patient C. S. (Case 3). The three limb leads are shown from above downward. The electrocardiographic tracing on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride. Inverted T waves in Leads I and II have now become upright.

Physical examination revealed the signs of cardiac failure including edema of the lower extremities. There was narrowing and tortuosity of the retinal arterioles. The urine contained 3 plus albumin and concentrated to 1.018. Phenolsulfonphthalein excretion was reduced. The electrocardiogram was interpreted as showing digitalis effects and left ventricular strain. There was cardiac enlargement and pulmonary congestion by roentgen ray.

The blood pressure, which was 190/140 on admission, fell to 170/120 several days after admission. The edema of the legs cleared after diuresis with mercupurin. Veratrum therapy was begun at a dosage level of 10 Craw units twice per day. The blood pressure in the supine position fell to 140/100, and in the standing position, to 120/90. He was discharged from the hospital on this dosage plus digitoxin 0.2 mg. daily, and in two months returned to work.

During the past seven months since discharge, the blood pressure ranged between 180/110 in the supine and 160/110 in the erect position. He experienced no further attacks of dyspnea or angina and has required no further treatment with either mercurial diuretics or nitroglycerin.

Roentgenographic examination of the heart six months after veratrum was begun showed reduction in cardiac size and clearing of congestive changes (Fig. 5). It was necessary gradually to increase the dosage of veratrum to 30 Craw units every twelve hours in order to maintain the hypotensive response. The patient was employed through a strenuous summer season with no evidence of cardiac failure. On one occasion veratrum was withdrawn for a period of five days. This was followed by a rise in blood pressure from 180/110 to 210/130 and an increase in pulse rate from 64 to 100 per minute. During this period the patient noted palpitation which promptly disappeared as soon as the drug was resumed.

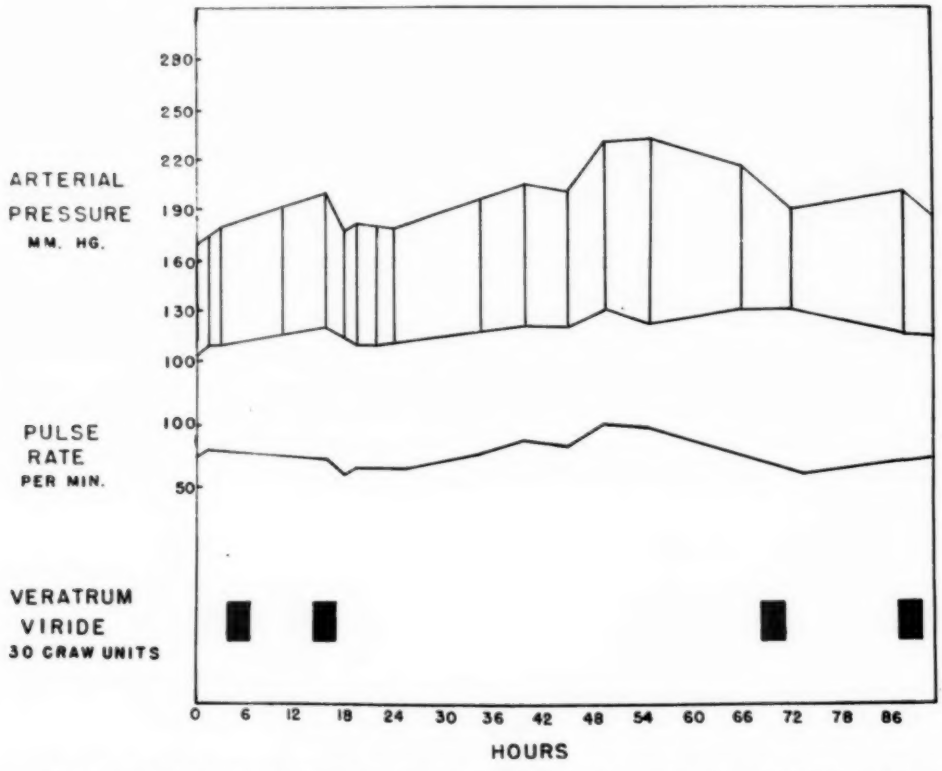

Fig. 4.—The effect of withdrawing medication in Patient C. S. (Case 3) who had been treated with veratrum viride continuously for seven months. Withdrawal of the drug was followed by elevation of the blood pressure and pulse rate which again fell following reinstitution of treatment.

Veratrum viride was also found to enhance the effectiveness of sympathectomy and of dietotherapy. The following case illustrates the effect of veratrum in a patient maintained on a low-salt diet.

CASE 5.—C. F., a 52-year-old white man, a shoe worker, suffered from headaches and dizzy spells for six months prior to his first visit to the outpatient department. Examination revealed the blood pressure to be 220/120, the heart to be slightly enlarged with no signs of failure, the retinal arteries to be narrowed and sclerotic, and renal function to be unimpaired, with no albuminuria and good concentrating ability.

Treatment with potassium thiocyanate was begun, but despite a blood level of 9 to 11 mg. per cent, maintained for one and one-half months, there was no reduction in the blood pressure and the patient complained of increased dizziness. Potassium thiocyanate was discontinued and

a low-salt diet instituted, salt-free milk powder* and salt-free bread being used. After one month on this regimen the blood pressure fell to 190/110 and the symptoms of headache and dizziness were relieved.

After the blood pressure had been stabilized at 190/110 on repeated clinic visits, veratrum was administered, the diet being continued meanwhile, and the dosage was gradually increased to 30 Craw units every twelve hours. One week after this dosage was attained the blood pressure was 160/100, fluctuating between this value and 175/110 during the next three months. When veratrum was withdrawn the blood pressure rose again to 190/110, promptly falling to 160/100 when the drug was readministered.

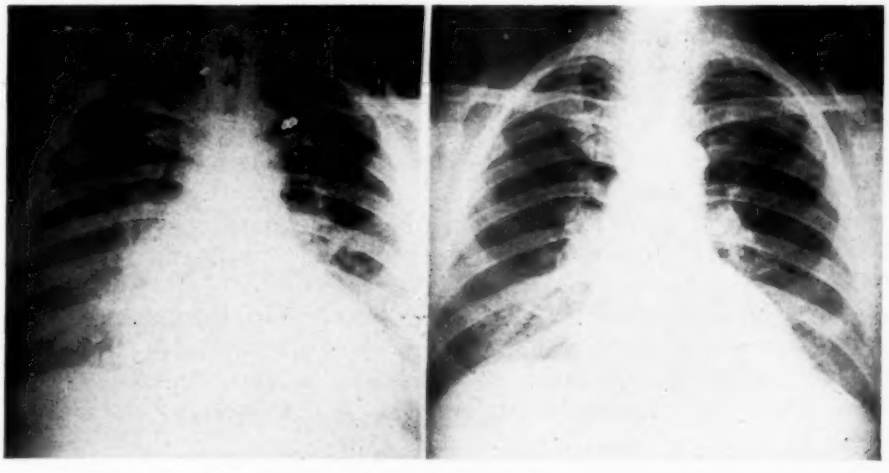

Fig. 5.—The reduction in cardiac size and clearing of pulmonary congestive changes in Patient R. Mc. (Case 4). The roentgenogram on the left was taken prior to treatment and that on the right was taken after seven months of continuous treatment with veratrum viride.

Toxic Reactions and Side Effects.—The reaction to a toxic dose of veratrum viride was in many ways similar to vasovagal collapse.[19] The pulse rate was slowed to between 45 and 60 beats per minute; the blood pressure was markedly reduced, and on one occasion fell to shock levels; there was sweating, nausea, repeated vomiting, salivation, collapse in the erect position, blurring of vision, mental confusion, and a sense of numbness in the extremities and around the mouth.† The bradycardia, but not the hypotension, was relieved by doses of 1.0 mg. of atropine sulfate administered intravenously. The hypotension could be abolished with ephedrine. These toxic reactions, although alarming to the patient, passed off in about five hours, leaving no residua. Such severe effects although largely avoided since the drug has been administered at intervals of eight hours or more, were sufficiently frequent to require careful and frequent observation of all patients under treatment.

Milder side effects occurred, such as nausea, transient blurring of vision, and a sensation of numbness, particularly about the mouth. In some cases, these effects appeared with and in some, before the hypotensive effects, necessitating

*Generously supplied under the name of "Lanolac" by the Mead Johnson Co., Evansville, Ind.

†Such a severe collapse, particularly when associated with a substernal burning sensation, may be mistaken for a coronary occlusion.

the discontinuation of treatment. Occasional attacks of nausea, although not uncommon, were seldom sufficient to cause withdrawal of the medication, but frequently necessitated readjustment of dosage.

The most frequent side effect was a sensation of epigastric burning occurring soon after the ingestion of each dose. This effect was not entirely due to local gastric irritation[1] since similar symptoms were observed following parenteral administration of veratrum viride.

Drug Tolerance.—The phenomenon of tachyphylaxis following the administration of veratrum in animals has been well documented.[5] Tachyphylaxis, apparently, is much less likely to occur with minimal effective doses than with large doses.[4,20] Clinically, in hypertensive patients the development of some degree of drug tolerance was occasionally observed. However, tolerance seldom became complete so that a considerable reduction in blood pressure could still be obtained at the end of twelve or more months of treatment. The typical dramatic result of short-term treatment has been described in Case 1, while the usual less marked hypotensive effect obtained after long-term therapy has been illustrated in Case 3. Occasional patients required less rather than more medication after long-continued treatment.

With continued administration of the drug at a constant dose level it was not unusual to note the sudden or gradual development of nausea and vomiting after days, weeks, or months. Following several such episodes these side effects passed off or in some cases persisted requiring a wider spacing or actual reduction in dosage. The possibility of combatting these developments with the use of tablets containing 5 rather than 10 Craw units, or tablets with enteric coatings, and/or by the use of atropine or hyoscine is under investigation at present.

Adjustment of Dosage.—Since the effective and toxic doses were quite variable in different patients, successful therapy depended upon gradually increasing the dosage in each case and necessitated repeated observations, especially during the early phases of treatment. The following methods of administering the drug were found to be most efficacious. The patient was given an initial dose of 10 Craw units after the morning and evening meals. Outpatients were seen in the clinic after several days of medication, the visit being so arranged that the blood pressure and pulse rate were recorded approximately four to six hours after the patient had received his last medication. Provided that neither a definite hypotensive response nor toxic reactions had occurred, the dosage was increased to 20 Craw units morning and evening administered in subdivided doses of 10 Craw units at hourly intervals, preferably separated by a meal. By such repeated observations of blood pressure, pulse rate, and symptoms, the dosage was increased gradually until a therapeutic effect or toxic reaction occurred.

In hospitalized patients a similar procedure was adapted, or the following more rapid method was used. The rapid method consisted in administering the drug in amounts of 10 Craw units at intervals of two hours while recording the blood pressure and pulse rate responses every half hour until a therapeutic or toxic effect occurred. Minor readjustments of dosage frequently were necessary after the patient had left the hospital.

DISCUSSION

The results of this investigation indicate that veratrum viride is useful in the treatment of certain cases of essential hypertension. The dramatic hypotensive response following short-term administration established the efficacy of the drug in the treatment of so-called "hypertensive crisis." In this condition veratrum was far more effective in our hands than the customary therapeutic methods of venesection or heavy sedation. In addition, the less dramatic but nevertheless significant and prolonged hypotensive effects of veratrum in several severely hypertensive patients, including some with cardiac failure, warrants the hope that such patients may receive lasting benefit from this therapy.

In less severe cases of hypertension, therapy with veratrum was not as useful as in the severe cases. Careful attention to dosage and frequent readjustment of dosage were necessary because of side effects and the development of drug tolerance. Therefore, the milder forms of essential hypertension were more effectively treated by diet, reassurance, sedation, and rest, and, in selected cases, by lumbodorsal splanchnicectomy.

However, cases of long-standing hypertension with marked elevations of blood pressure, not benefitted significantly either by diet or surgery, and more or less incapacitated by the disease, were compensated for the occasional toxic reactions to veratrum by the relief afforded from the symptoms of the disease. In such cases the combined use of a salt-free diet and veratrum viride proved to be more efficacious than either therapeutic agent used alone.

SUMMARY AND CONCLUSIONS

1. Veratrum viride in the form of the whole powdered mixture of alkaloids was administered orally to a series of forty patients with essential hypertension for periods up to thirteen months.

2. When the drug was administered by the oral route, the hypotensive effect began to appear at the end of one or two hours, reached a maximum in four or six hours, and largely disappeared by the end of fourteen hours. In order to obtain maximum therapeutic benefit and to avoid toxic reactions resulting from cumulative overdosage, veratrum was administered at dosage intervals of twelve hours. In addition, in order to provide greater therapeutic safety, this dosage interval was further subdivided so that no more than 10 Craw units were ingested per hour. The great variability of response to a given dose in different individuals required the gradual increase of dosage in each patient in order to avoid toxic side effects.

3. Veratrum was found to be a useful therapeutic agent in the treatment of patients with (a) "hypertensive crisis," (b) severe, long-standing hypertensive disease which proved resistant to other forms of treatment, and (c) hypertension complicated by cardiac failure.

4. Prolonged therapy in some cases resulted in a diminution in cardiac size and reversal of electrocardiographic changes toward normal.

5. There were no deaths and no toxic reactions resulting in more than transient disability attributable to the drug. However, the development of

side effects and of changing sensitivity to a given dose were sufficiently frequent to limit its usefulness in the treatment of patients with mild or moderate degrees of hypertension.

6. Veratrum viride appeared to have therapeutic value as an adjunct to dietotherapy and to the routine treatment of hypertensive heart disease.

The authors wish to thank Dr. Robert W. Wilkins for active cooperation and guidance throughout the period of this study.

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THE EFFECT OF POSTURE UPON AXIS DEVIATION IN HUMAN BUNDLE BRANCH BLOCK

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OUR interest in this subject arose from a case of bundle branch block in which serial records showed rather remarkable changes in axis deviation. In Fig. 1, Records *A*, *B*, *C*, *D*, and *E* are consecutive standard limb lead electrocardiograms taken for routine purposes over a period of eighteen months; Records *A*, *C*, and *E* show prolongation of QRS and left axis deviation and were reported as left bundle branch block, whereas Records *B* and *D* show prolonged QRS and right axis deviation and were therefore believed to represent right bundle branch block. We[1] have shown elsewhere that neither right nor left bundle branch block causes great changes in the direction of the mean electrical axis of QRS, so that, even if the side of the block did alternate in this remarkable way, it seems unlikely that this could account for such great changes of axis. In searching for an alternative explanation, we recalled that Ackerman and Katz showed that in experimental bundle branch block in the dog, changes in posture could reverse the direction of QRS in either Lead I or Lead III,[2] and that in human bundle branch block, turning the patient to the left lateral position could reverse the direction of QRS in Lead III, so that discordant left bundle branch was changed to the concordant type.[3] Although the changes in our patient were much more striking, for QRS was reversed in both Lead I and Lead III, it seemed worth while to explore the possibility that even these changes could be due to alterations in the position of the heart. This proved to be the explanation, for with the patient in the supine posture, typical left bundle branch block was present (Fig. 1,*F*) and when the patient turned into the left lateral posture, right axis deviation and apparent right bundle branch block appeared (Fig. 1,*G*).

These observations led us to undertake the present study with the object of discovering how frequently such striking postural changes of axis occur in human bundle branch block. It also seemed advisable to exclude the rather unlikely possibility that the side of the block had actually changed from left to right, for in our patient we had not taken adequate precordial leads in the left lateral posture.

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METHODS

The criteria used for the diagnosis of bundle branch block were those we have previously enumerated.[1] In forty otherwise unselected cases which fulfilled these requirements, twenty patients with right bundle branch block and twenty with left, we have recorded the standard limb leads and Goldberger's augmented unipolar limb leads (aV leads)[4] in the supine, right lateral, and left lateral positions. In addition, in the supine posture, the side of the block was determined from precordial leads recorded by Wilson's technique[5] in the six standard positions,[6] but when left bundle branch block was suspected, a seventh precordial lead was recorded in the posterior axillary line at the level of the fourth, fifth, and sixth standard positions (Lead V_7). In ten of these patients, including all those in whom there could be any suspicion that the side of the block had changed with alteration in posture the precordial V leads were repeated in the two lateral postures. In all instances gross delay in the appearance of the intrinsic deflection[7] was demonstrated on one side of the precordium only; there is, therefore, no doubt of the side of the block in any of these patients.

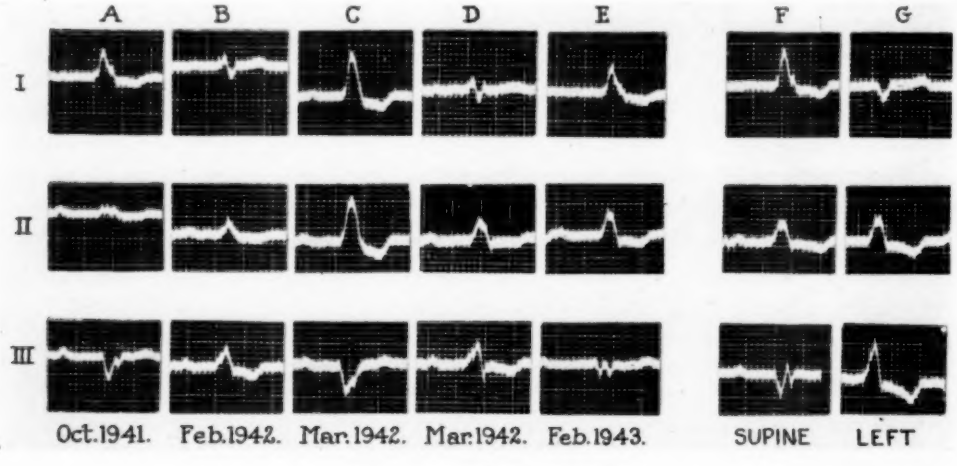

Fig. 1.—*A*, *B*, *C*, *D*, and *E* are standard limb lead electrocardiograms showing apparent alternation of right and left bundle branch block in consecutive records. *F* is an electrocardiogram taken in the supine posture showing left bundle branch block; *G* is taken on the same occasion with the patient in the left lateral posture and shows apparent right bundle branch block. Presumably, these postural changes account for the variations in *A*, *B*, *C*, *D*, and *E*.

Measurement of Axis Position.—By Dieuaide's method,[8] the position of the electrical axis was measured in the standard limb leads with the patient in the supine, right, and left lateral postures. A representative number of complexes was measured, and if the axis position varied with respiration, the extremes were measured and the average recorded. For descriptive purposes we have accepted as the normal axis position the arbitrary limits of 0° to +90° proposed by Carter and associates.[9]

The Electrical Position of the Heart.—From Leads aV_L and aV_F the electrical position of the heart was determined in each posture by the method of Wilson and his collaborators.[10]

RESULTS

Left Bundle Branch Block (Twenty Cases).—

Changes of Axis Position: Changes of axis of 30° or less seemed unlikely to be of much practical importance, and in twelve of twenty cases, alterations of posture did not cause axis changes exceeding that amount. In the remaining eight cases, the axis position shifted more than 30° when the patient moved from the supine into one or other lateral posture; in three cases this occurred when the patient turned into the right lateral posture, in three, with assumption of the left lateral posture, and in two cases, with assumption of either lateral posture (Table I). Six of these shifts of axis exceeded 60°; in one instance (Case L 18) the axis rotated 129° to the right when the patient turned into the left lateral position, and in another patient (Case L 19), assumption of the right lateral posture caused the electrical axis to rotate 185° to the right, while turning from the supine into the left lateral posture caused almost as great a rotation in the same direction (173°). With one exception (Case L 12) all shifts of axis exceeding 30° on the assumption of a lateral posture were to the right.

Changes of Axis Classification: In the supine posture the electrical axis fell within normal limits in seven of twenty cases; in the remaining thirteen cases abnormal left axis deviation was present. In the lateral postures the axis classification remained unchanged in fourteen cases. Of three patients with normal axis position in the supine posture, two (Cases L 2 and L 13) remained within normal limits in the right lateral posture and changed to abnormal right axis deviation in the left lateral posture. In the remaining patient (Case L 12) the normal axis position was unaltered in the left lateral posture but abnormal left axis deviation appeared in the right lateral posture. In three patients with abnormal left axis deviation in the supine posture, two (Cases L 8 and L 18) fell within normal axis limits in the right lateral posture and in the left lateral posture one of these reverted to abnormal left axis deviation (Case L 8) and the other changed to abnormal right axis deviation. In the remaining patient (Case L 19) with abnormal left axis deviation in the supine posture, abnormal right axis deviation was present in both lateral postures.

Changes of Electrical Position of the Heart: In the supine posture the electrical position, determined from the augmented unipolar limb leads, was horizontal in twelve cases, semihorizontal in two cases, intermediate in four cases, and semivertical in two cases. In fourteen cases changes of posture did not alter the electrical position. Of three patients with hearts in the horizontal position in the supine posture, two (Cases L 8 and L 18) assumed an intermediate electrical position in the right lateral posture, and in the left lateral posture one became semihorizontal and the other (Case L 18), vertical; in the remaining patient (Case L 19), the electrical position changed from the horizontal to the vertical when either lateral posture was assumed. Two patients with intermediate

TABLE I. THE EFFECT OF CHANGES IN POSTURE UPON THE ELECTRICAL AXIS, THE ELECTRICAL POSITION OF THE HEART, AND THE ELECTROCARDIOGRAPHIC PATTERN

CASE	AXIS POSITION			AXIS CLASSIFICATION			ELECTRICAL POSITION			EFFECT ON ECG PATTERN	
	S (DEGREES)	RIGHT (DEGREES)	LEFT (DEGREES)	S	RIGHT	LEFT	S	RIGHT	LEFT	TURNING TO RIGHT	TURNING TO LEFT
L 2	+40	+53	+116	N	N	R	Int.	SV	V	—	Reversal QRS_I
L 7	+16	+56	+43	N	N	N	Int.	Int.	Int.	Discordant to concordant	Discordant to concordant
L 8	−12	+24	−25	L	N	L	H	Int.	S. H.	—	—
L 12	+ 8	−33	+20	N	L	N	S. H.	S. H.	S. H.	—	—
L 13	+40	+44	+110	N	N	R	S. H.	S. H.	V	—	Reversal QRS_I
L 18	−10	+30	+119	L	N	R	H	Int.	V	Discordant to concordant	Reversal QRS_I
L 19	−35	+150	+138	L	R	R	H	V	V	Reversal QRS_I	Reversal QRS_I
L 20	+ 6	+ 8	+ 38	N	N	N	Int.	Int.	SV	—	Discordant to concordant

S = supine posture
Right = right lateral posture
Left = left lateral posture
N = normal position of mean electrical axis of QRS (0° to +90°)
L = abnormal left axis deviation
R = abnormal right axis deviation

V = vertical electrical position
SV = semivertical electrical position
Int. = intermediate electrical position
S.H. = semihorizontal electrical position
H = horizontal electrical position

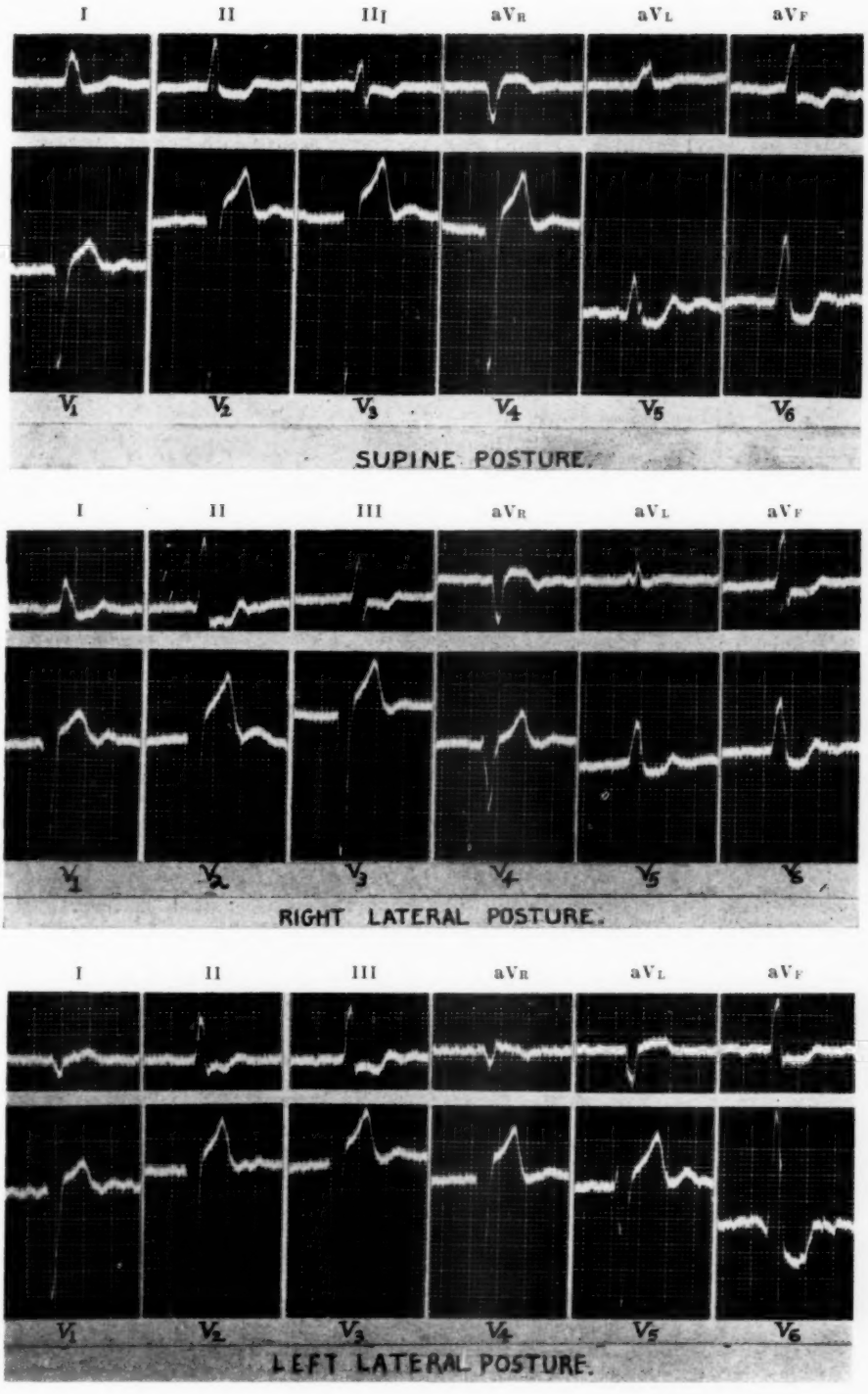

Fig. 2.—Case L 2; left bundle branch block. In the supine posture the pattern is concordant and the position of the heart (aV_L and aV_F), intermediate. In the right lateral posture, the pattern remains concordant. In the left lateral posture, right axis deviation and apparent right bundle branch block appear; the electrical position becomes vertical, but the precordial leads continue to indicate delay of the intrinsic deflection over the left precordium (Lead V_6).

electrical positions in the supine posture assumed semivertical positions in the right lateral posture and vertical positions in the left lateral posture. The remaining patient, with an intermediate electrical position (Case L 20), retained this in the right lateral posture, but assumed a semivertical position in the left lateral posture.

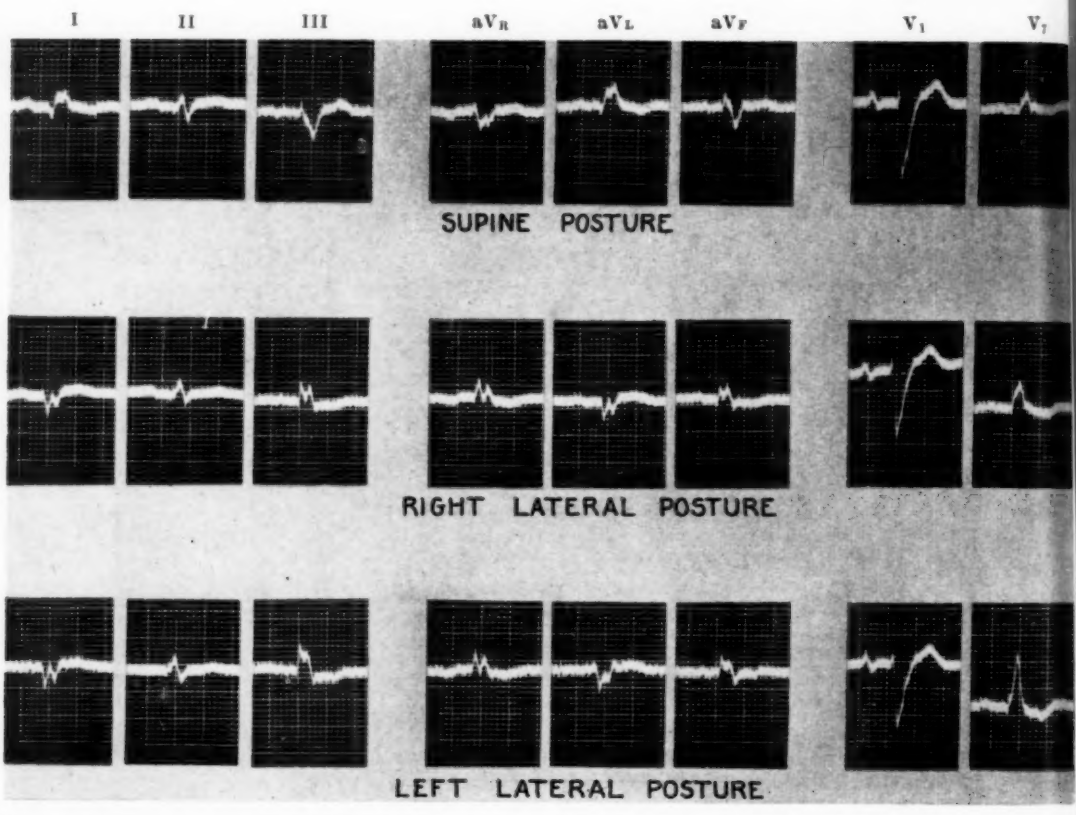

Fig. 3.—Case L 19; left bundle branch block. In the supine posture the pattern is discordant and the electrical position of the heart horizontal. In both lateral positions right axis deviation and apparent right bundle branch block appear, and the electrical position becomes vertical, but precordial leads V_1 and V_7 continue to indicate left bundle branch block.

Effects Upon the Electrocardiographic Pattern: There were striking changes in the general appearance of the electrocardiogram in six cases. In four cases a positive QRS in Lead I became negative, leading to a change from left to right axis deviation, a wide S wave in Lead I, and apparent reversal of the side of the block; in three patients this occurred only on moving into the left lateral posture (Cases L 2, L 13, and L 18) but in one patient (Case L 19) the assumption of either lateral posture was effective. In three cases a negative QRS in Lead III became upright, so that the pattern changed from the discordant to the concordant type of left bundle branch block; this occurred, when the left lateral

posture was assumed (Case L 20), in the right lateral posture (Case L 18), in both lateral postures (Case L 7). The changes in Cases L 2, L 19, L 18, L 20, and L 7 are shown in Figs. 2, 3, 4, 5, and 6, respectively, and all striking changes are summarized in Table I.

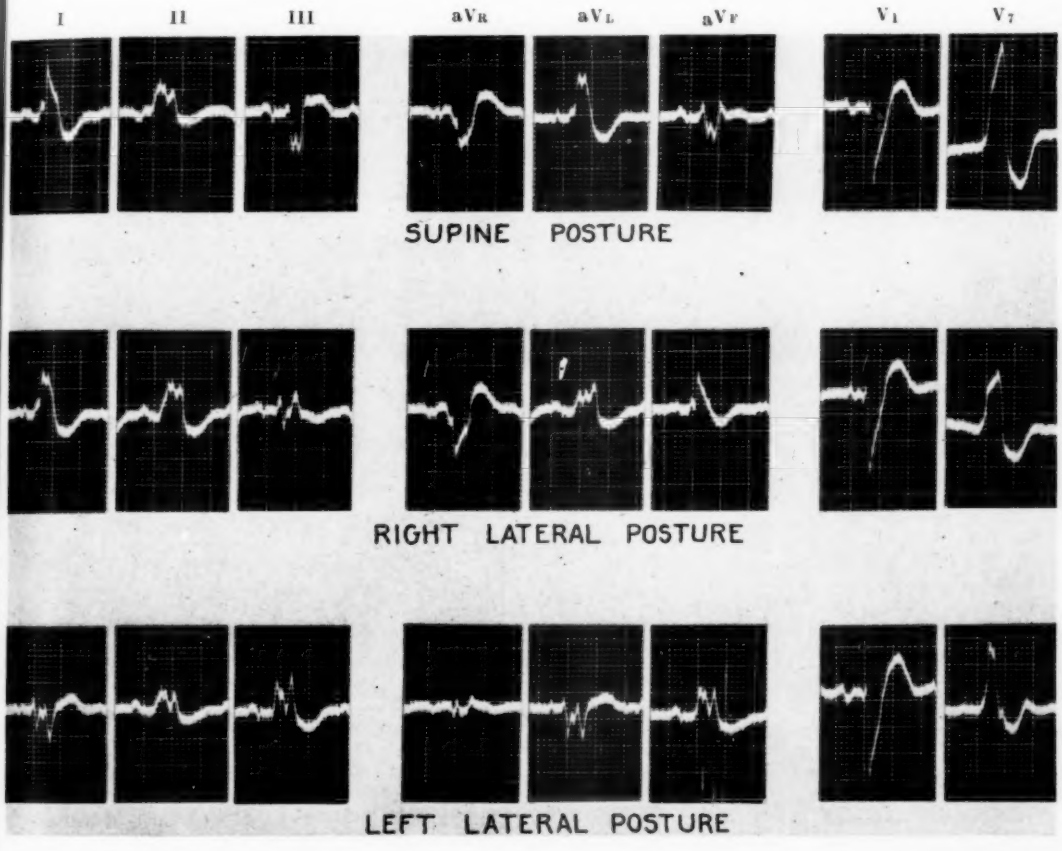

Fig. 4.—Case L 18; left bundle branch block. In the supine posture the pattern is discordant and the electrical position horizontal. In the right lateral posture the pattern is concordant and the electrical position intermediate. In the left lateral posture, right axis deviation and apparent right bundle branch block appear and the electrical position becomes vertical. Chest Leads V_1 and V_7 show left bundle branch block in all postures.

Precordial Leads: All of these changes in the standard and augmented unipolar limb leads occurred without significant changes in the precordial V leads which showed delay of the intrinsic deflection over the left precordium in all postures. In Figs. 2, 3, and 4, right and left precordial leads are illustrated in all postures in the three patients with the most striking limb lead changes (Cases L 2, L 18, and L 19).

Summary: To summarize the postural changes in left bundle branch block: The side of the block, as judged by the standard limb leads, was reversed in one-

fifth (four) of our cases. This reversal was affected most often by assumption of the left lateral posture. The discordant type of left bundle branch block was converted to the concordant type rather less frequently (three cases). Posture did not alter the side of the block when this was decided by precordial leads.

Right Bundle Branch Block (Twenty Cases).—Our observations in right bundle branch block were less striking.

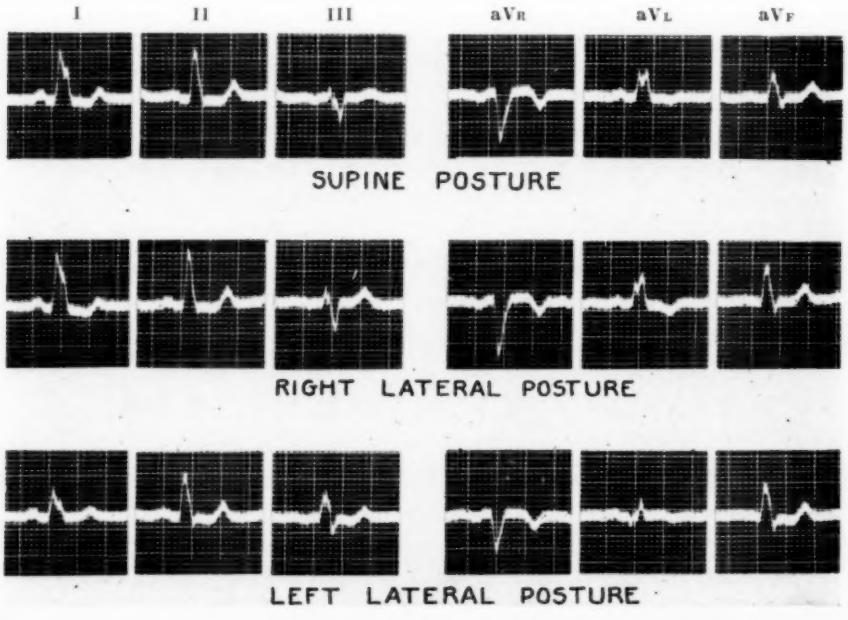

Fig. 5.—Case L 20; left bundle branch block. In the supine posture the pattern is discordant and the electrical position intermediate. There is no material change in the right lateral posture, but in the left lateral posture the pattern becomes concordant because of inversion of QRS in Lead III, and the electrical position becomes semivertical.

Changes of Axis Position: In thirteen patients the postural change of axis was 30° or less; in the remaining seven a change of axis of more than 30° occurred, twice on the assumption of the right lateral posture and five times on turning onto the left side. In only one instance did the axis shift exceed 60° (Case R 16) and in that patient a change in Lead III from a positive QRS of 1.0 mm. to a negative deflection of 1.5 mm. was principally responsible for an axis shift of 110° to the left. This was the sole instance in which assumption of either lateral posture led to leftward rotation of the electrical axis.

Changes of Axis Classification: In the supine posture there were six patients with right bundle branch block with abnormal left axis deviation, nine with normal axis position (0° to +90°), and five with abnormal right axis deviation (more than +90°); changes of posture altered the axis category in only one patient (Case R 16), in whom a normal axis position in the supine posture was converted to abnormal left axis deviation when the left lateral posture was assumed.

Changes of Electrical Position of the Heart: In none of our patients with right bundle branch block was the electrical position changed by alteration of posture.

Effects Upon the Electrocardiographic Pattern: In three patients assumption of the left lateral posture led to standard limb lead records that were difficult to interpret, for the wide S wave in Lead I disappeared. Apart from this, there were no striking changes, and in no instance did the standard limb lead electrocardiogram simulate the appearance of left bundle branch block.

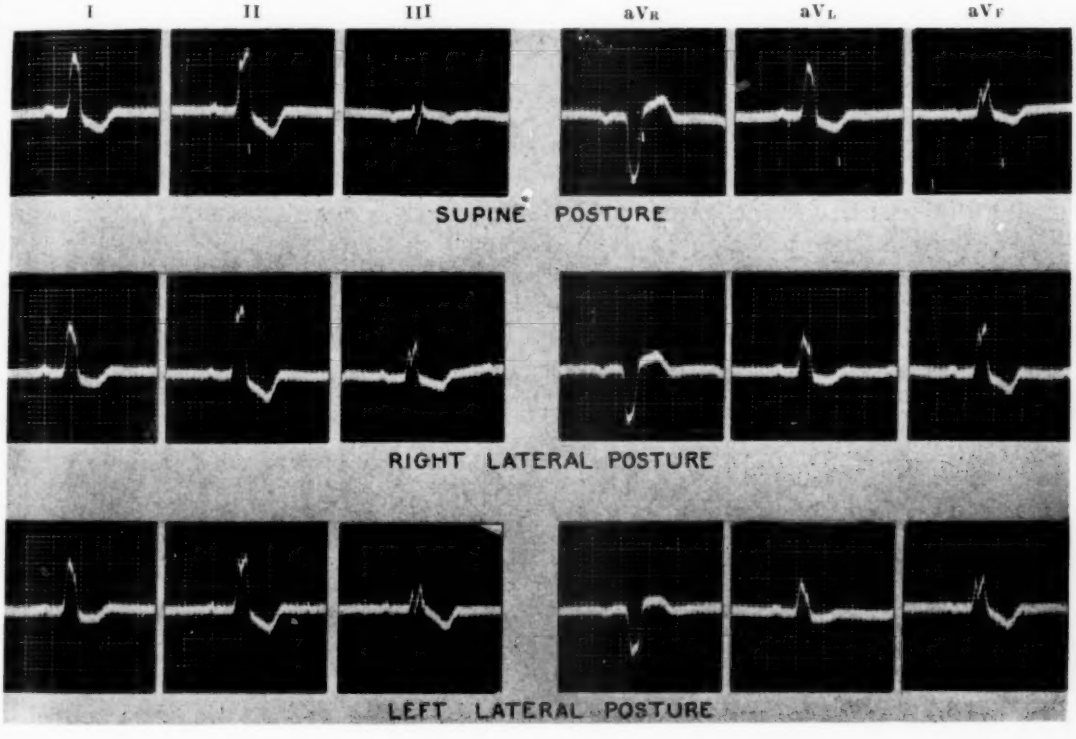

Fig. 6.—Case L 7; left bundle branch block. In the supine posture the pattern tends to be discordant and the electrical position is intermediate (with QRS greater in Lead aV_L than in Lead aV_F). In the right and left lateral postures the pattern is concordant but the position remains intermediate, though QRS is now greater in Lead aV_F than in Lead aV_L.

DISCUSSION

From our observations of these patients we conclude that in left bundle branch block alterations of posture not infrequently cause gross rotation of the electrical axis to the right, the assumption of a vertical electrical position of the heart, and a reversal of the direction of QRS in Lead I so that the standard limb leads come to simulate right bundle branch block. A lesser degree of rightward rotation of the electrical axis leads to conversion of the discordant type of left

bundle branch block to the concordant type. These changes in the standard and unipolar limb leads are not accompanied by any significant change in the characteristic precordial patterns of left bundle branch block.

In 1933, Ackerman and Katz[3] showed that in human left bundle branch block, assumption of the left lateral posture converted the discordant pattern to the concordant in two of six patients, but they were unable to duplicate in human bundle branch block the more striking postural changes they had previously found in experimental canine bundle branch block.[2] They concluded that it was unjustifiable to attempt to locate human bundle branch block from the appearances of the standard limb leads, but this conclusion was strongly criticized by Foster,[11] who pointed out that none of the postural changes produced in man by Ackerman and Katz were sufficiently great to lead to difficulty in deciding the side of the block. Foster claimed also that to produce apparent reversal of the side of the block in the dog required a rotation of axis of 180° and believed this to be most unlikely in man under clinical conditions. Our observations indicate that such changes of axis occur in man not infrequently as a consequence of simple alterations of posture and, probably rarely, even when routine electrocardiograms are made without attempting to alter posture. We, therefore, agree with Ackerman and Katz in their assertion that the standard limb lead electrocardiogram may be unreliable as an indication of the side of the block. Fortunately, since their work, the introduction of multiple unipolar precordial leads has provided a reliable method of localizing the side of the block in the majority of cases, and our observations indicate that the value of this method is not diminished if changes of posture occur. We are, therefore, no longer compelled, as Ackerman and Katz believed, to consider abandoning in man the terminology of right and left bundle branch block.

It seems remarkable that axis shifts as great as 180° (Case L 19) can be produced by the simple expedient of turning onto the side. Certainly there could not be so great a rotation of the heart upon its anteroposterior axis; evidence has now accumulated to indicate that other factors are involved. Lewis,[12] in his study of a patient with a rifle bullet embedded in the heart, was able to compare the movement of the anatomic axis radiographically with the changes of the direction of the electrical axis; he found that when the anatomic axis, as indicated by the bullet, moved 6° to 8°, the shift of the electrical axis was 20°. It is, therefore, unnecessary to assume that the shift of the anatomic axis must correspond in magnitude with the electrical axis shift. An explanation for this discrepancy may be found in the work of Meek and Wilson,[13] who observed that simple rotation of the heart on its anteroposterior axis produced much less striking changes in the electrical axis than rotation of the heart upon its long axis. From the extent of the changes in axis in our patients, it seems probable that the latter type of rotation plays a large part in the effects of posture upon the position of the electrical axis. In addition, it is known that the electrical conductivity of tissues contiguous to the heart affects the distribution of cardiac action potentials.[14,15] It is necessary, therefore, to envisage the possibility that changes in the position of the heart may alter its relationship to tissues of differing conduc-

tivity and, in this way, affect the potential differences recorded at the limb roots and, as a result, the appearances of the unipolar and standard limb leads.

From a practical point of view, we consider that our results indicate once again the importance of a standard posture in recording the electrocardiogram, provide yet another example of the fallacy of attributing significance to the axis deviation as an indication of the side of bundle branch block, and emphasize the reliability of adequate precordial leads in deciding this point.

SUMMARY

1. A case of bundle branch block is described in which the block apparently alternated between the right and left branches. The changes in the electrocardiographic pattern were subsequently duplicated by alteration of the patient's posture.

2. The effect upon the standard and augmented unipolar limb leads and upon the precordial leads of changing from the supine to either right or left lateral postures has been studied in forty cases of bundle branch block, twenty of the right and twenty of the left bundle branch.

3. The position of the electrical axis has been measured in each case in the three postures and the electrical position of the heart determined from the augmented unipolar limb leads.

4. In left bundle branch block the axis shifted more than 30° in eight of nineteen cases; in six instances the shift exceeded 60°. The greatest shift was 185°. The direction of shift was, with one exception, invariably to the right on assumption of a lateral posture. The electrical position of the heart became more vertical in all six patients in whom it was altered.

5. In four patients with left bundle branch block, an upright QRS in Lead I became negative so that right axis deviation and apparent right bundle branch block appeared in the lateral posture. In three patients assumption of a lateral posture caused a negative QRS in Lead III to become upright so that the discordant pattern of left bundle branch block became concordant. In all of these patients the precordial leads showed delay in the intrinsic deflection over the left precordium in all postures.

6. In right bundle branch block, assumption of one or the other lateral posture led to a shift of axis of more than 30° in seven of twenty patients; in six of these, the shift was to the right. In no case did the electrocardiographic pattern simulate left bundle branch block, and the electrical position of the heart was never grossly altered.

7. It is concluded that the limb leads are unreliable as a guide to the side of bundle branch block in some cases, but that the precordial leads are little affected by changes of posture. The importance of taking electrocardiograms in a standard posture is re-emphasized.

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DETERMINATION OF THE LEVO- AND DEXTROCARDIOGRAM

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THE fundamental work of Lewis[1] and of Wilson and Herrmann[6] has shown that the electrocardiogram represents the algebraic summation of two distinct components, the levo- and the dextrocardiogram. These left and right components usually appear at the same time, but they can be dissociated when bundle branch block exists. This dissociation is not total, however, because activity always begins in one ventricle before it ends in the other. Moreover, in such a case the invasion of the second ventricle takes place through abnormal pathways. For these reasons, the curves of bundle branch block do not allow an exact determination of the levo- and dextrocardiogram. However, if the bundle branch block is incomplete, the curves can be used for this purpose, since in this case the invasion of the incompletely blocked ventricle follows the usual conduction pathway. Incomplete bundle branch block is often a transient condition, so that normal complexes may also be recorded in the same patient. When these two types of curves are available, the levo- and dextrocardiogram can be calculated in the following manner.

Let us call V_1, V_2, V_3 . . . . the successive values of the cardiac potentials, as they can be measured 0.01, 0.02, 0.03 . . . . second after the beginning of the ventricular electrocardiogram. Each of these potentials is to be considered as the algebraic sum of a right and a left ventricular component which we may call, respectively, D_1, D_2, D_3 . . . . and L_1, L_2, L_3 . . . . In the normal electrocardiogram, when these two components begin simultaneously,

$$V_1 = D_1 + L_1 \quad ; \quad V_2 = D_2 + L_2 \quad ; \quad V_3 = D_3 + L_3 \ldots . \quad (1)$$

If an incomplete left bundle branch block* develops, the recorded tracing will be different, the successive values of the ventricular potentials becoming V'_1, V'_2, V'_3 . . . .

If the invasion of the left ventricle begins with a delay of 0.01 second, then

$$V'_1 = D_1 \quad ; \quad V'_2 = D_2 + L_1 \quad ; \quad V'_3 = D_3 + L_2 \ldots . \quad (2)$$

As V_1, V_2, V_3 . . . . and V'_1, V'_2, V'_3 . . . . are known, it can be seen that the equations obtained in (1) and (2) make it possible to calculate all the successive values of the levo- and dextrocardiogram.

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*The case of left bundle branch block has been chosen for consideration because left bundle branch block is more favorable for the purposes of this discussion than right bundle branch block.

METHOD

Correct calculations can be made only if the exact value of the delay in left ventricular activation can be determined from the curve of incomplete bundle branch block. This is done by recording the normal then the abnormal electrocardiogram in Leads I, II, III, and CR_5 simultaneously. The time that elapses between the beginning of the earliest QRS wave in any one of the limb leads and the moment at which the intrinsic deflection occurs in Lead CR_5 are measured, first in the normal, then in the abnormal electrocardiogram. The difference between the two values represents the delay in left ventricular activation in the case of incomplete bundle branch block.

This determination can be checked by a different method, provided that the same patient also shows complexes of complete left branch block. The very beginning of the curves of complete and incomplete left bundle branch block is identical in shape and represents a true dextrocardiogram. The moment when these two curves begin to differ indicates the onset of the levocardiogram in the complex of incomplete branch block, and the value of the left ventricular delay is thus known.

The normal and abnormal complexes have been recorded in the same tracing while the patient holds his breath; the incomplete bundle branch block is usually induced by a slight acceleration of the sinus rhythm or by auricular extrasystoles. The complexes of interest to this study have been enlarged by means of a projection lantern and redrawn on a millimetric scale. The successive values of the electrical potentials in the different leads have thus been measured with an accuracy of 0.03 millivolt at intervals of 0.01 or 0.005 second. The value of the left ventricular delay has generally been established with an accuracy of 0.003 second.

RESULTS

Fig. 1 shows the enlarged records of the QRS deflections of a normal and an abnormal beat, both obtained in the same patient. Lead CR_5, not reproduced here, shows that the intrinsic deflection occurs 0.014 second later in the abnormal than in the normal complex. From these data the QRS deflections of the levo- and dextrocardiogram were calculated and the results are shown in the same figure.

Similar determinations have been made in ten patients with transient incomplete left bundle branch block and the results are in general agreement with those of the particular case reported here. When the electrocardiogram does not show any important axis deviation, the levo- and dextrocardiogram are never very different from each other. Their general contour is approximately the same as that of the normal electrocardiogram, except that their voltage is lower,

The most characteristic features are that in Leads I and II the levocardiogram shows Q but no S waves, whereas the dextrocardiogram shows S but no Q waves. It may be concluded, therefore, that in Leads I and II of the normal electrocardiogram, Q and S correspond, respectively, to left and right ventricular activity. This confirms the observation made previously by Sodeman and coworkers[3] concerning the origin of the Q wave of Lead I.

The manifest value of R is higher and the orientation of its axis is slightly more to the left for the levocardiogram than for the dextrocardiogram (Fig. 2). The rotation of the electrical axis generally occurs in a clockwise direction in both levo- and dextrocardiogram. Fig. 1 does not picture the S-T segment or the T wave because they do not show any particularity: the S-T segment is isoelectric and the T waves of Leads I and II are upright in both the levo- and dextrocardiogram.

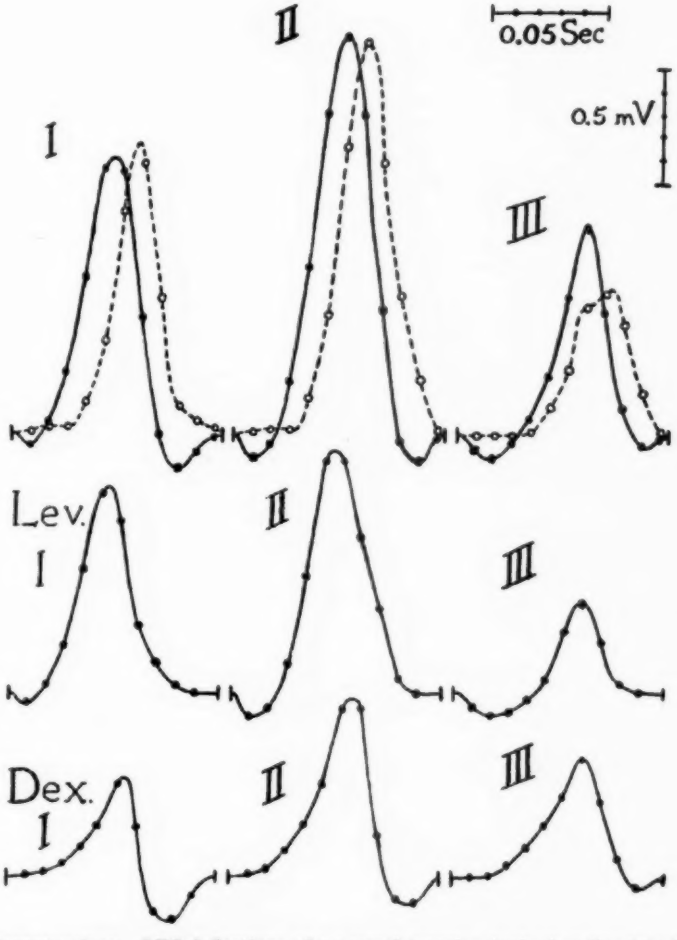

Fig. 1.—*Upper tracings*: **QRS deflections of a normal complex (unbroken lines) and of a complex with incomplete left branch block (broken lines), recorded in the three limb leads simultaneously. Vertical lines at the beginning and at the end of QRS indicate synchronous moments in the three leads.**
Lower tracings: **Calculated QRS deflections of the levo- and dextrocardiogram.**

The same patient also shows occasional complexes of complete left bundle branch block. If these are recorded and enlarged by the same procedure and the already calculated dextrocardiogram is subtracted from these complexes, the difference reveals the pathologic levocardiogram of the bundle branch block type (Fig. 3). This figure is completely different from that corresponding to the

normal invasion of the left ventricle. There is a very marked left axis deviation (Fig. 2), the duration of QRS is about 0.10 second, the rotation of the electrical axis is counterclockwise in direction, T_1 is inverted, and the S-T segment is displaced in a direction opposite to the QRS deflection. The onset of this pathologic levocardiogram occurs 0.02 to 0.03 second later than the onset of the normal dextrocardiogram, although the delay in the activation of the left ventricle amounts to 0.05 second. This discrepancy results from the longer duration of the invasion.

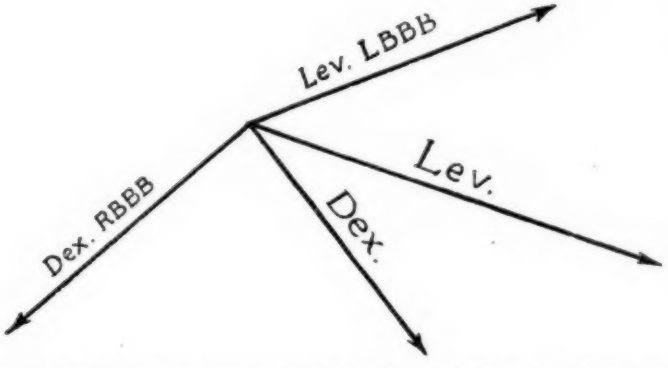

Fig. 2.—Manifest value and axis orientation of the R wave in the normal levo- and dextrocardiogram and in the pathologic levo- and dextrocardiogram of the bundle branch block type.

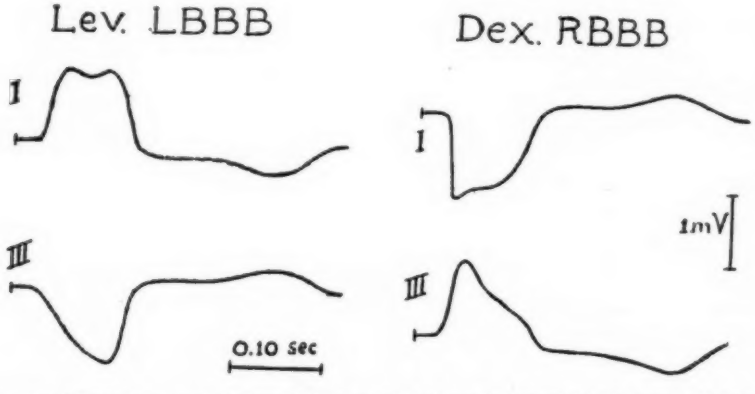

Fig. 3.—Pathologic levo- and dextrocardiogram of the bundle branch block type in Leads I and III. The curves are calculated by subtraction of the normal dextro- and levocardiogram from the recorded left and right bundle branch block electrocardiograms.

In another patient with transient incomplete left bundle branch block whose levo- and dextrocardiogram had been calculated, some complexes of complete right bundle branch block of the uncommon type were also recorded. By subtraction of the levocardiogram from this latter curve, the pathologic dextrocardiogram represented by Fig. 3 was obtained. This curve is definitely abnormal: there is an important right axis deviation (Fig. 2), the duration of QRS

is about 0.10 second, the rotation of the electrical axis takes place in a clockwise direction, and the S-T segment is displaced upward in Lead I.

These levo- and dextrocardiograms of the bundle branch block type correspond to the curves formerly obtained by several authors, but it is obvious that they do not correspond to a normal ventricular invasion.

DISCUSSION

The accuracy of this method of determining the levo- and dextrocardiogram can be proved by the following fact. If the algebraic summation of the right and left components is made with different degrees of delay of the levocardiogram with regard to the dextrocardiogram, the calculated curves reproduce exactly the recorded electrocardiogram of different degrees of incomplete bundle branch block (Fig. 4). This correlation between the calculated and the recorded curves remains very close as long as delay on the left does not exceed 0.02 to 0.03 second.

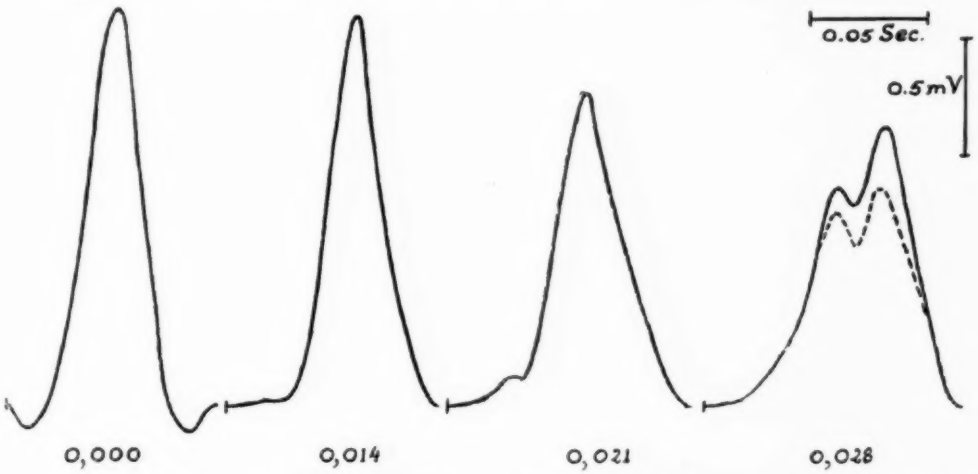

Fig. 4.—Patient showing different degrees of incomplete left bundle branch block. Unbroken line: One normal QRS complex and three QRS complexes with various degrees of left ventricular delay recorded in Lead II. Broken line: Calculated curve for the corresponding degrees of delay of the levocardiogram with regard to the dextrocardiogram. The two lines are perfectly superimposed and therefore indistinguishable as long as the left ventricular delay does not exceed 0.021 second (the left delay is indicated in seconds under each complex).

This method of calculation of the levo- and dextrocardiogram assumes that the invasion pathway is not altered in incomplete bundle branch block. The fact that the recorded curves really satisfy Equations 1 and 2 clearly demonstrates the validity of this assumption. On the other hand, we have previously recorded the vectocardiogram of incomplete left bundle branch block,[2] and the curve does not reveal any notching characteristic of an abnormal pathway of conduction,[4] provided that the delay does not exceed 0.02 to 0.03 second.

These facts indicate that an abnormal pathway of invasion exists when the delay in the bundle branch exceeds 0.02 to 0.03 second. It is, therefore, probable that in this case the left ventricle is simultaneously activated through the normal

and an abnormal pathway, and that the levocardiogram represents a kind of mixed beat. These conclusions are in accord with the fact that in complete left bundle branch block the pathologic levocardiogram begins 0.02 to 0.03 second after the onset of the normal dextrocardiogram.

It has been assumed in Equation 1 that the onset of the levo- and dextrocardiogram is simultaneous in the normal electrocardiogram. This is certainly not always correct, but even if there is normally a slight delay of the levocardiogram, this does not modify the validity of the set of equations: in such a case it would simply be found by the calculations that the value of L_1 is zero. Simultaneous recording of Leads CR_2 and CR_5 in this series of ten cases often revealed the other eventuality, a slight delay of the dextrocardiogram.

The curves obtained here show that the normal levo- and dextrocardiogram must no longer be considered as mirror images with opposite axis orientation. This view arose because the former conception of the levo- and dextrocardiogram was based upon a study either of pathologic bundle branch block or upon the monopolar mode of derivation.[5] Since these curves of bundle branch block are the result of an abnormal mode of invasion or of a particular mode of exploration of the heart, they cannot be used to reconstruct the normal electrocardiogram.

SUMMARY

A method of determining the normal levo- and dextrocardiogram is described.

The levo- and dextrocardiogram are very similar to a normal bicardiogram but of lower amplitude. The main difference between them is that in Leads I and II the levocardiogram shows a QR and the dextrocardiogram, an RS deflection. The manifest value of R is higher and the angle αR somewhat smaller for the levo- than for the dextrocardiogram. The rotation of the electrical axis usually occurs in a clockwise direction for both.

These results do not substantiate earlier concepts concerning the levo- and dextrocardiogram.

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FURTHER EXPERIENCE WITH THROMBOANGIITIS OBLITERANS IN WOMEN

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ALTHOUGH thromboangiitis obliterans in women is still a rare disease,[1-10] recent experience appears to show that it is occurring with increasing frequency. In the first 1,000 patients with this disease seen by the writer, there were only two women,[6] but in the last 600 there have been twenty-three women. Although the incidence for the entire group is only slightly over 1 per cent, in the past ten years it has risen to 4 per cent.

During the past twenty-five years women increasingly have adopted the habit of smoking, and many of them smoke excessively. Since, in my opinion, the use of tobacco by individuals susceptible to this substance is the etiological factor causing thromboangiitis obliterans,[11] it is not difficult to understand why more women are showing signs of this illness. Furthermore, this trend is likely to become more pronounced in the future. Physicians must be alert to the possibility that circulatory disease of this type is present when young female patients complain of discomfort in the extremities.

This presentation is based upon the study of twenty-five female patients with thromboangiitis obliterans seen in private and clinic practice. The essential criterion used in making this diagnosis was the presence of symptoms and signs of obliterative vascular disease in the extremities in women between the ages of 20 and 45 years. A history of intermittent claudication, coldness of the extremities or change of color with different positions of the extremities was usually present in varying degree. The occurrence of superficial phlebitis or painful ulcerations of the fingers or toes with operative or spontaneous loss of digits or amputation of the extremities in persons in this age group gave added weight to the diagnosis of thromboangiitis obliterans. Absence of some major pulsations in the upper or lower extremities was noted in nearly all cases. Evidence of impairment in the circulation was confirmed by oscillometric studies in all cases and by temperature studies in some.

In order to exclude individuals with peripheral vascular disease due to arteriosclerosis, patients with diabetes, gout, or syphilis were not considered in this series. These disorders are known to hasten the development of arteriosclerosis. Hypertension militated against the inclusion of a case when it was clear that an

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elevated blood pressure had existed prior to the appearance of symptoms of arterial obstruction. Individuals in whom calcified vessels could be visualized by x-ray films were excluded. Arteriosclerotic vascular disease without x-ray evidence of calcification is frequently present in patients who first present symptoms of impaired circulation between the ages of 45 and 55 years, and such cases were not included in this series.

CASE HISTORIES*

CASE 1 (1529).—H. B., an American Hebrew woman, 29 years of age when first seen in 1932, was in perfect health until August, 1931. While stepping out of the water at a beach she felt pain in her left leg which was so severe that she was unable to walk for an hour. She then limped home. Following this episode she continued to have intermittent claudication in the left leg after walking three blocks. In December, 1931, she had been treated by a chiropodist for an ingrown toenail. Gangrene of the left great toe, associated with severe pain, developed. This extended and involved the first and second toes and an extensive portion of the dorsal surface of the left foot. Because of severe pain, nerve section to produce anesthesia of the involved area was carried out by another surgeon. Following this, amputation of the first and second toes was done. In the course of time a granulating wound formed and the foot healed completely. This patient had smoked twenty cigarettes a day for a number of years but discontinued smoking with the onset of the present illness. She was married and had two children.

Examination in December, 1933, showed a young woman in good health except for the condition in the lower extremities. The circulation in the upper extremities was normal. The left femoral artery was open. The left popliteal artery was closed. There was no pulsation in the left foot. All normal pulsations were present in the right foot. The left first and second toes were missing and there was a well-healed scar over this portion of the foot. The oscillometer readings were: left calf, 1.5; left ankle, very faint; right ankle, 2.5. The basal metabolic rate was −11 per cent. Blood volume was 63 c.c. per kilogram. The serum cholesterol was 250 mg. per cent and calcium, 12 mg. per cent. Skin tests showed sensitivity to tobacco, ragweed, and timothy. She continued to show improvement and when examined in 1937 was able to walk any distance without trouble. The pulses in her feet remained unchanged, but the oscillometer readings were improved.

This patient was last seen in May, 1946. She stated that she could walk any distance and had no further trouble with her legs. Her left foot had remained healed. All pulses were present in the right foot, none in the left. The oscillometer readings were: right ankle, 3; left ankle, 0.5.

This is a typical example of a female patient with thromboangiitis obliterans who has never resumed smoking and who has had no recurrence of trouble in her legs in a period of observation of fourteen years. Considerable impairment of circulation persists in the left leg, but function is not impaired for ordinary purposes.

CASE 2 (1936).—M. S., an American Hebrew woman, 33 years of age when first seen in November, 1933, had had attacks of superficial phlebitis on the right leg for the past six years. There had been three such attacks and evidence of the last one was still present. Five weeks previously the left great toe had become swollen and painful. Pain was severe at night. For the past five years there had been some discomfort in walking. Her menses were regular, usually lasting two to three days. She was married and had two children. She had been smoking fifteen cigarettes a day for the past seven years. Examination revealed a healthy young woman with the exception of the extremities. The radial vessels were open on both sides. The ulnar pulses could not be felt on either side, and the Allen test was confirmatory of obstruction in these vessels. Both femoral and both popliteal pulses were present. No pulsation was felt in either foot. The right foot showed marked rubor in the dependent position and striking pallor on elevation. There was evidence of recent phlebitis on the inner side of the left ankle. The tip of the right great toe was tender and there was a fissure at this point. The oscillometer readings were: left calf,

*The first two cases in this series have been published previously.[6]

4.5; left ankle, 1.5; right calf, 3; right ankle, 0.75. Skin tests showed sensitivity to tobacco and ragweed.

No data are available on the subsequent history of this patient.

CASE 3 (2651).—J. B., an English-born Hebrew woman, was 29 years of age when first seen in 1936.

She had had discomfort in the left leg for one year, worse on standing and walking, and could walk only one block without stopping. She had been smoking twenty cigarettes a day for the past five or six years. She was married and had one child. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral and both popliteal arteries were open. All pulses were present in the right foot. There was no pulse in the left foot. There was pallor of both feet on elevation more marked in the left. There was marked rubor of the left lower extremity in the dependent position. The oscillometer readings were: left calf, 2.5; left ankle, 0.25; right calf, 6; right ankle, 3. Blood volume was 70 c.c. per kilogram. Chemical examination of the blood revealed cholesterol of 340 mg. per cent. The Wassermann test was negative. She was advised to stop smoking and was treated with intravenous injections of 5 per cent saline solution twice a week. Her walking gradually improved and she was able to walk six blocks without discomfort. Saline injections were stopped in 1937.

In March, 1940, about three years after the last visit, she was seen again. She reported that during the past one and one-half years she had resumed smoking. Two months prior to this examination she had struck her right great toe against a chair and an ulceration developed which became larger. She had considerable pain in that foot. At that time there was no pulsation in either foot. The oscillometer readings were: left calf, 0.25; left ankle, 0; right calf, 0.25; left ankle, 0. The right foot showed marked rubor. Both feet were cold. There was a shallow ulcer on the inner side of the right first toe, 2.0 cm. in diameter. She was again advised to stop smoking and to resume saline injections. She was treated for several months with considerable improvement. The ulcer healed and pain was relieved. There was still no pulsation in either foot, but the oscillometer readings had improved and were: left calf, 0.5; left ankle, faint; right calf, 1; right ankle, faint. She was seen again in December, 1945. She stated that she had had no further trouble with her legs and could walk any distance without pain. She does not smoke.

This patient is a typical instance of thromboangiitis obliterans in a woman. When first seen she presented only moderate impairment of circulation in the legs, and she improved quickly under treatment. When she resumed the use of tobacco, the disease was rapidly aggravated, and when seen again she had advanced circulatory impairment in both legs. It is now six years since she has stopped smoking. She is in good condition and has had no further trouble with her legs.

CASE 4 (3609).—H. L., an American gentile woman, was 38 years of age when seen in 1938. She gave a history of having been a heavy drinker and smoker for many years. Two years prior to the examination she had had a stroke involving the left side of the body, particularly the face and arm. She recovered from this condition, but there was a persistent sense of numbness in the left hand. For about one and one-half years she had had intermittent claudication in the left leg after walking three blocks. About two weeks before she was first studied she suddenly developed pain in the right leg and when she was seen, the pain was so severe that she was unable to walk at all. She could not sleep without drugs. Wassermann tests had been repeatedly negative. She was married but had no children.

Examination showed a well-nourished woman. The general physical examination was essentially negative. Her blood pressure was 120/70. Circulation in the upper extremities was normal. Both femoral arteries were open. Both popliteal arteries were closed. There was no pulsation in either foot. There was pallor on elevation and rubor in the dependent position of both feet, more marked on the right side. The anterior half of the right foot was very sensitive to pressure. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 0.5; right ankle, very faint. The further history of this patient is not known.

This is a typical example of thromboangiitis obliterans in a gentile woman, the first of our female patients who showed cerebral involvement.

CASE 5 (3456).—D. W., a Russian Hebrew woman, was 35 years of age when first seen in 1938. She stated that ten months previously while walking home from the beach she had suddenly felt pain in the left calf. She was able to walk only one-half block thereafter without pain in this leg. There was a history of postoperative phlebitis in the left leg seventeen years previously. For eight months she had been taking thyroid capsules and pituitary extract for reduction of weight. She smoked about twenty cigarettes a day. She was married and had two children. Examination showed a markedly obese woman. The blood pressure was 154/94. General physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral arteries were open, but the pulse in the left femoral artery was small. The right popliteal pulse was present; the left was absent. There was no pulse in the left foot. All pulses were present in the right foot. The oscillometer readings were: left calf, faint; left ankle, 0; right calf, 10; right ankle, 5. She was instructed to stop smoking and to reduce her weight, but no other treatment was recommended.

This patient was next seen in January, 1945. She stated that she had stopped smoking for three years and that during this time had felt very much better. She then had begun to smoke again and for the past two years she had been unable to walk more than one block because of pain in the *right* leg. Re-examination showed an obese woman who was 100 pounds overweight. Circulation in the upper extremities was normal. The left femoral pulse was present; the right was very small. The popliteal pulses could not be felt. The left dorsalis pedis pulse was present. There was no other pulse in the left foot and there was now no pulse in the right foot. The oscillometer readings were: left calf, 1.5; left ankle, 0.5; right calf, 1; right ankle, faint. Her blood pressure had risen to 170/105. X-ray films of the legs showed no calcification of the blood vessels. A blood cholesterol determination was normal. In May, 1946, a report was obtained from her physician who stated that she continued to maintain good health.

This patient developed hypertension subsequent to the appearance of peripheral vascular disease in her legs. There were no signs of arteriosclerosis anywhere in her body. Usually the blood pressure is normal or below normal in thromboangiitis obliterans. However, hypertension in the later stages of the disease has been observed by the writer in several instances.

CASE 6 (3724).—B. G., an American Hebrew woman, was 30 years of age when first seen in 1939. She stated that four weeks previously, while walking on the street on a very cold day, she suddenly developed pain in both lower extremities and her legs became paralyzed. She was taken home by car and had to be carried to her bed. Her feet were cold and white. She continued to have pain for several days. Mild heat was used over the legs. She developed purplish spots on the tip of the right great toe and at two other places on the right foot. These discolored spots became blisters which opened and discharged. In August, 1938, she had had a transient left hemiplegia with a facial paralysis which persisted for some weeks. She entered another hospital where a diagnosis of arteritis of unknown etiology was made. She had been married nine years and had two healthy children. She had been smoking about twenty cigarettes a day for five years. Examination showed a well-nourished, healthy looking young woman. General physical examination was negative except for slight residual weakness of the left side of the body. Her blood pressure was 100/70. Circulation in the upper extremities was normal, except that the left radial pulse was somewhat smaller than the right. The left femoral artery was open; the right was closed. Both popliteal arteries were closed. There was no pulse in either foot. There was a blister at the tip of the right first toe and two small red spots on the dorsal surface of the right foot. The oscillometer readings were: left wrist, 1; right wrist, 1.5; left calf, 0.75; left ankle, 0; right calf, 0.5; right ankle, 0. Blood chemical tests were normal. The Kline test was negative. The basal metabolic rate was −16 per cent. An electrocardiogram was negative. X-ray films of the legs showed no calcification in the blood vessels. She was advised to avoid weight bearing until the foot healed, to stop smoking, and to sleep under a thermoregulated heater.

The last report on this patient by her family physician, in September, 1945, stated that her condition was greatly improved since she had stopped smoking; her walking had improved; both feet were warm. The pulses were still absent. She had received no active therapy.

This is a typical instance of thromboangiitis obliterans in a young Jewish woman which is notable because the first clinical manifestation of the disease was a right cerebral thrombosis.

CASE 7 (39-7176).—G. A., an American Hebrew woman, was 26 years of age when first seen at The Mount Sinai Hospital in 1939. She complained of red, tender lumps on both legs of six months duration, but had no other symptoms. She was smoking twenty cigarettes daily. Her general physical examination was entirely negative. All pulsations were present in both upper extremities. All pulsations were present in the left foot. The right posterior tibial pulse was absent. The right anterior tibial and dorsalis pedis pulses were present. The oscillometer readings were: left calf, 3.5; left ankle, 2; right calf, 2; right ankle, 2. There was some swelling of the right ankle and foot and evidence of a superficial phlebitis on the inner side of the right leg. A diagnosis of thromboangiitis obliterans was made and she was advised to stop smoking. No other treatment was recommended. Her condition improved. The inflammation on the right leg cleared up and she was able to walk any distance without pain. However, she began to gain considerable weight and for this reason she resumed smoking in 1941.

When next seen in December, 1944, she reported that for six months she had had pain in the left calf after walking one block. Examination at that time showed the left popliteal artery to be closed and no pulse in the left foot. The right posterior tibial and dorsalis pedis pulses were absent. The right anterior tibial pulse was present. The oscillometer readings were: left calf, 0.25; left ankle, very faint; right calf, 3.5; right ankle, 1.5. At this time she stopped smoking and treatment was begun with intravenous injections of 5 per cent sodium chloride solution three times a week. She showed steady improvement and in June, 1946, she was able to walk one-half mile without pain. The pulsations were unchanged, but the oscillometer readings were: left calf, 1; left ankle, 0.5; right calf, 4; right ankle, 1.5. She then again resumed smoking and developed a small, infected ulcer on the plantar surface of the left foot. She was admitted to The Mount Sinai Hospital in March, 1947. With cessation of smoking, rest, and wet dressings, her condition rapidly improved. In September, 1947, her condition was good. She was again able to walk one-half mile without pain.

The diagnosis was made in this case at a stage when only one foot pulse was absent. If this patient had accepted the advice to avoid smoking permanently, she could have spared herself much later trouble.

CASE 8 (5619).—J. M., an unmarried German Jewish refugee woman, was 37 years of age when first seen in April, 1940 in the wards of The Mount Sinai Hospital. Seven years previously she had first begun to have pain in the left foot on walking which was relieved by rest. She also had some tingling in the hands in cold weather. Four years previously she had had a Leriche operation on the left femoral artery, with some relief of pain. She was under marked tension and nervous strain during 1937 and 1938. In 1938, she first began to notice pain in the right leg. At that time a Leriche operation was done on the right side without much benefit. Six weeks previously she had developed pain in the right great toe. She kept her leg constantly dependent and it became swollen. She had been smoking at least fifteen cigarettes daily, and frequently more.

Examination showed a well-developed and well-nourished woman who sat most of the time on the side of the bed with both feet hanging down. She complained of constant severe pain. General physical examination was essentially negative. Blood pressure was 104/60. Both brachial pulsations were present. The right radial pulse was small. The right ulnar artery was closed. A small pulse was present on the back of the right hand. There was no pulse in the left wrist. The right femoral pulse was present; the left was absent. Both popliteal arteries were closed and there was no pulse in either foot. There was marked edema of both legs due to the dependent position of the legs. There was an ulcer of the right first toe. The oscillometer readings were: left arm, 3.5; right arm, 4; left wrist, 0.25; right wrist, 0.5; both calves and both ankles, faint. She stopped smoking and was treated with typhoid vaccine injections and sedatives. The ulcer was dressed with cod liver oil ointment. Her condition gradually improved and she was discharged from the ward in June, 1940. Treatment was continued in the Peripheral Vascular Disease Clinic where she received intravenous injections of hypertonic saline solution three times a week. The ulcer healed completely in August, 1940, and her ability to walk improved. Treatment was discontinued in June, 1941.

Following some emotional disturbance, she resumed smoking in 1942, and in December of that year she developed an ulcer on the right first toe. At this time the oscillometer readings in the left and right calves were zero. She was readmitted to the hospital and again was treated with saline injections for a month. However, the ulcer persisted in spite of various forms of conservative treatment. In December, 1944, she was admitted to the Montefiore Hospital where an amputation of the distal half of the left first toe was done. The toe healed slowly and was completely healed in February, 1946. She is now able to walk two blocks without pain and is doing full-time work. There is still no pulse in either foot and the oscillometer readings are unchanged.

This patient was first seen when the circulation in all four extremities was severely affected by thromboangiitis obliterans, and she was suffering severely with an ulcer of the great toe. This healed under treatment, but in spite of her previous painful experience, she resumed smoking and brought on a recurrence of ulceration.

CASE 9 (4897).—H. W., an American Hebrew woman, 20 years of age when first seen in 1941, complained of a swollen and painful foot after an accident. The pain was constant and severe. X-ray films of the foot were negative. On physical examination pulsations of the dorsalis pedis vessels were absent. All other pulses were present in both feet. She smoked from twenty to forty cigarettes daily.

In October, 1944, this patient returned with the history that for one year there had been numbness of the left foot on walking one block and difficulty in dancing because of pain in the left foot. She was married but had no children. Examination showed some atrophy of the left calf. The left popliteal artery was closed and there was no pulse in the left foot. The right popliteal and posterior tibial pulses were present; the right anterior tibial and dorsalis pedis pulses were absent. The oscillometer readings were: left calf, 0.5; left ankle, faint; right calf, 3; right ankle, 1. The left foot was cool and showed typical rubor in the dependent position. The circulation in the upper extremities was normal. She was advised to stop smoking and to have saline injections. She was treated irregularly for two months and showed some improvement in walking. When she was last seen in April, 1945, the same pulses were present but the oscillometer readings were: left calf, 1; left ankle, 0.25; right calf, 4; right ankle, 1.75.

Thrombosis of the popliteal artery occurred in this young woman at the age of 22 years. It is not unusual for thromboangiitis obliterans to start at this early age.

CASE 10 (5533).—M. H., a Russian-born Hebrew woman, was 30 years of age when first seen in October, 1942. For two and one-half years she had had pain in the left lower extremity on walking, and for one year she had been able to walk only ten steps without stopping. A painful ulcer had been present on the left third toe for a few months. She had started to smoke at the age of 16 years and had been smoking twenty cigarettes a day since then. She was married and had one child. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both femoral and both popliteal arteries could not be felt. There was a small right posterior tibial pulse. No other pulse could be felt in either foot. The oscillometer readings were: left calf, faint; left ankle, 0; right calf, 1; right ankle, 0.5. There was a small superficial ulcer about 0.5 cm. in diameter on the outer side of the left third toe. The left foot was much cooler than the right. She was advised to stop smoking and a course of intravenous saline injections was instituted. She showed steady improvement; in December, 1942, the ulcer was almost healed, there was practically no pain, and she was able to sleep without medication. Treatment was continued until May, 1944, at which time she was in excellent condition.

This patient was last seen in June, 1946, and was still in good condition. However, her brother had been killed in the war about a year before, at which time she had resumed smoking. She was warned that she was inviting further trouble.

This patient, like so many others, illustrates the difficulty of weaning individuals permanently from the tobacco habit. Although they admit they realize the danger to their health, any upsetting emotional experience causes them to "reach for a cigarette," and soon they are smoking heavily again.

CASE 11 (5944).—E. B., an American Hebrew woman, was 31 years of age when first seen in 1943. For three years she had had pain in the left calf and foot on walking. She had been smoking twenty cigarettes a day since the age of 14 years. She was married and had three children. The general physical examination was essentially negative. Circulation in the upper extremities was normal. Both posterior tibial pulses were absent. Both anterior tibial and the left dorsalis pedis pulses were present. The right dorsalis pedis pulse was absent. The oscillometer readings were: left ankle, 1.5; right ankle, 3.5. Both feet were fairly warm. She was advised to stop smoking. No other treatment was recommended. In September, 1945, she reported by letter that her condition was much better. However, she has never returned for examination.

CASE 12 (6111).—B. S., an American Hebrew woman, was 33 years of age when first seen in September, 1943. She stated that she had had blueness of the hands for seven years and of the feet for two years. Two and one-half years previously she had had an ulcer of the right index finger which took over one year to heal. This recurred and again took one year to heal. Later she developed gangrene of the left index finger and lesions on her left thumb and fifth finger which also healed slowly. Four months previously she developed an ulcer on the right third finger. This was extremely painful and was not relieved by large doses of sedatives. There was no history of any trouble with walking. She had begun to smoke at the age of 15 years and smoked about a package of cigarettes a day. She had been taking four grains of thyroid extract daily because of overweight and had also received pituitary extract. A body rash had been present for the past seven years. She was married but had no children at the time she was first seen; she had had one miscarriage. However, she had a normal pregnancy and delivery in 1945.

Examination showed a considerably overweight young woman. The general physical examination was negative. The right hand was considerably swollen. The thumb and fifth fingers were normal. The end of the second finger was scarred. There was an ulcer about 1.0 cm. in diameter over the outer side of the right middle finger overlying the distal joint; this was covered with a scab. There was a similar lesion on the inner side of the fourth finger also overlying the joint. The tip of the fourth finger was scarred. The right radial pulse was present; the right ulnar pulse was absent. The left hand was not swollen. The tips of all the fingers were cyanotic. The tip of the left fifth finger was slightly scarred. There was an ulcer 3.0 mm. in diameter on the palmar surface of the terminal phalanx of the left thumb, covered with a scab. The area was extremely tender. The left radial pulse was present; the left ulnar pulse was absent. The toes of both feet were somewhat cyanotic. All pulses were present in both feet, but were small.

The oscillometer readings were: left ankle, 1; right ankle, 1. There was an extensive patch of dermatitis on the back with a sharply defined margin. The skin was reddened and slightly scaly. There was a similar area over the pubis and on the left thigh. The blood Wassermann was negative. An electrocardiogram was normal. X-ray films of the right hand showed no abnormality in the bones or soft tissues. She was advised to stop smoking and to stop the use of thyroid extract and sedatives; typhoid vaccine, intravenously, and cod liver oil ointment for the ulcers were recommended. On this treatment she began to show steady improvement. When she was seen in November of the same year, the pain was entirely relieved and the ulcers on the second and fourth fingers were healed. There was a granulating wound on the middle finger about 1.5 by 2.5 centimeters. She was now advised to have saline injections intravenously in place of the typhoid vaccine, and with this treatment the fingers healed completely. In February, 1944, she returned with a small blisterlike lesion on the tip of the right fourth finger which had been present for about two weeks. The other fingers remained healed. This lesion gradually became larger and she was again treated with typhoid vaccine injections. The finger healed and she was not seen again until September, 1945. At this time she had a painful ulcer on the left third finger. She has not returned for examination since then.

This patient illustrates to a striking degree the tendency of women patients with thromboangiitis obliterans to have serious involvement of the upper extremities before there are symptoms in the feet. In this case, an erroneous diagnosis of Raynaud's disease was accepted by the writer on a first casual examination, but this error was quickly recognized when symptoms persisted. As soon as the true nature of the condition was realized and proper treatment instituted, rapid improvement took place.

CASE 13 (7277).—R. G., an unmarried American Hebrew woman, was 30 years of age when first examined in The Mount Sinai Hospital in May, 1943. At that time she complained that for one year she had had attacks of pain in both feet. She was smoking ten cigarettes a day. Her general physical examination was negative. Circulation in the upper extremities was normal. The right anterior tibial and posterior tibial pulses were normal. The right dorsalis pedis pulse was absent. The left anterior tibial pulse was normal. The left posterior tibial and dorsalis pedis pulses were absent. The left foot was slightly cooler than the right. There was slight blanching of the left foot on elevation and both feet were somewhat redder than normal in the dependent position. The oscillometer readings were: left calf, 6; left ankle, 2; right calf, 7; right ankle, 3. A diagnosis of incipient thromboangiitis was made, and she was advised to stop smoking. No other treatment was recommended. However, she continued to smoke.

She was seen again in February, 1945, when she complained of pain in the left calf after walking two blocks and of pain in the toes which interfered with sleep. Examination showed marked progression of the vascular disease in the legs. Both femoral pulses were present. The right popliteal pulse was present; the left was absent. The right posterior tibial pulse was present. There was no other pulse in either foot. The oscillometer readings were: left calf, 0.5; left ankle, 0; right calf, 4.5; right ankle, 2. She had an ulcer on the plantar surface of the left foot. At this time treatment with intravenous injections of 5 per cent saline solution was started. By June, 1945, the ulcer had healed and she was able to walk three blocks without stopping. She complained of dizziness and headaches following the injections of saline and these were, therefore, discontinued.

On her last examination in June, 1947, she was able to walk four blocks without stopping. The right posterior tibial pulse was present. In addition, there was a right peroneal pulse. The right anterior tibial and dorsalis pedis pulses were still absent. There were no pulses in the left foot. The oscillometer readings were: left calf, 1; left ankle, 0.25; right calf, 4.5; right ankle, 2.25.

This patient, like the patient in Case 7, was seen at a time when her circulatory disease was incipient. She refused to follow advice against tobacco and returned with serious impairment of circulation.

CASE 14 (7641).—S. S., an American Hebrew woman, was 29 years of age when first seen at The Mount Sinai Hospital in 1943. Her only complaint was of coldness and pain in the right third finger. She stated that she had first begun to smoke *at the age of 9 years*, and that in recent years she had been in the habit of smoking twenty cigarettes a day. She was married and had one child. The involved finger remained persistently cold even when the feet were kept in hot water for forty-five minutes. All pulsations were present at both wrists and in both feet. A diagnosis of incipient thromboangiitis obliterans involving only the digital vessels of the right third finger was made. Cessation of smoking was advised but no other treatment was recommended. She stopped smoking for about one year and her symptoms disappeared, but she resumed smoking because she was gaining weight.

She was seen again in June, 1945, when she complained of pain in her right leg after walking one and one-half blocks. The general physical examination was negative. The left ulnar pulse was absent. All the other pulses were felt in both upper extremities. All pulsations were present in the left lower extremity. The right femoral pulse was present. The right popliteal pulse was absent and there was no pulse in the right foot. The oscillometer readings were: left calf, 5; left ankle, 3; right calf, 1; right ankle, faint. There was hypesthesia of the right foot and blanching on elevation. She was again advised to stop smoking and treatment with saline injections was instituted. Her condition thereafter showed steady improvement. On last examination, in January, 1947, she stated that she was able to walk four blocks without pain. All pulses were present in the left foot, and a small dorsalis pedis pulse could be felt in the right foot. The oscillometer readings were: left ankle, 2.5; right ankle, 0.5.

This case is interesting because of the onset of thromboangiitis obliterans in the right upper extremity at a time when there were no symptoms or signs of vascular disease in the legs.

CASE 15 (44-1157).—T. P., a Hebrew woman, was 24 years of age when first seen at The Mount Sinai Hospital in March, 1944. For one and one-half years she had had pain in the left

calf after walking five blocks or after dancing. She had been smoking twenty cigarettes a day. She was married but had no children. Examination showed a well-nourished young woman whose general physical examination was negative. The right radial and left ulnar pulses were absent. The right ulnar and left radial pulses were present. Both femoral pulses were present. The right popliteal and right posterior tibial pulses were present. The right anterior tibial and dorsalis pedis pulses were absent. The left popliteal artery was closed and there was no pulse in the left foot. The oscillometer readings were: left calf, 0.5; left ankle, 0.25; right calf, 4; right ankle, 1.5. Blood pressure was 120/70. Blood Wassermann test was negative. It was difficult to persuade this patient to stop smoking, but she finally gave up using tobacco and was treated with intravenous injections of hypertonic salt solution. She showed steady improvement. In June, 1947, she was able to walk indefinitely without pain and without stopping. The pulses in her feet and the oscillometer readings remained unchanged.

This young woman, like the woman in Case 8, had thromboangiitis obliterans involving all our extremities.

CASE 16 (7322).—A. E., an Austrian-born Hebrew woman, was 41 years of age when first seen in February, 1945. In 1942, she began to have burning pain in the right first toe, and in 1944, developed an ulcer on this toe. This ulcer healed after three months of treatment with bed rest, injections of typhoid vaccine, Papaverine, Depropanex, and the use of regulated heat. Recently, the ulcer recurred and ulceration of the fourth toe of the same foot also developed. She had had intermittent claudication for one year. She had smoked twenty cigarettes a day for fourteen years. She was married but had no children.

On examination the left radial pulse was present; the ulnar pulse was absent. The Allen test was positive in the left hand. The right radial pulse was very small; the ulnar pulse was absent. There was a pulse on the dorsal surface of both wrists on the ulnar side. Both femoral arteries were open. The left popliteal pulse was present; the right was absent. The left anterior tibial pulse was present. There was no other pulse in either foot. The oscillometer readings were: left calf, 4; left ankle, 1.25; right calf, 0.25; right ankle, faint. There was tenderness of the right first and fourth toes with evidence of recent infection. There was marked rubor of the right foot and it was cooler than the left. She was advised to stop smoking, to avoid weight bearing, and to have saline injections. When she was last heard from in June, 1946, her ulcers were healed and she could walk five blocks without pain. She stated that she had given up smoking.

CASE 17 (7435).—I. Y., an American Hebrew woman, was 29 years of age when first examined in 1945. Eight years previously she had had a superficial phlebitis of the left leg, and intermittent claudication had developed shortly afterward. In 1942, she had developed gangrene on the inner side of the right great toe. In 1943, she had had a right hemiplegia with aphasia. Ever since then she has had occasional short epileptic attacks involving the right side and characterized by clonic contractions lasting a few seconds; she has also had crying spells. She had begun to smoke when very young and smoked twenty cigarettes a day. She had stopped smoking in 1943. She was married but had no children.

Examination showed a well-nourished young woman. There was weakness of the right side of the face and a hemiparesis of the right side of the body. She had almost complete motor aphasia but could speak a few words. There appeared to be no sensory aphasia. Her blood pressure was 130/80. Both radial arteries were open, but the ulnar arteries were closed. Both femoral arteries were open. Both popliteal arteries were closed. There was no pulse in either foot. There was a scar on the inner side of the right great toe. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 0.25; right ankle, 0. When she was last examined in June, 1947, her condition was unchanged.

This young woman with typical thromboangiitis obliterans of all four extremities presented the extremely unusual complication of a right hemiplegia and motor aphasia, which had developed at the age of 27 years. Two other women in this series (Cases 4 and 6) showed cerebral involvement.

CASE 18 (7483).—F. Z., an American Hebrew woman, was 42 years of age when examined in April, 1945. She had complained of pain in the left lower extremity on walking for fifteen years.

She was able to walk only one block, slowly. She also had a little trouble in the right leg. Six months previously she had had a lesion on the left index finger and a swelling on the inside of the wrist. She had begun to smoke at the age of 16 years and smoked from twenty to thirty cigarettes a day. She had stopped smoking three months previously and since then the condition of her hands had improved. She was married and had two children.

The general physical examination was essentially negative. All normal pulses were absent in the right wrist, but two abnormal pulses were present on the back of this wrist. The left radial pulse was present; the ulnar pulse was absent. There was moderate rubor of the toes of both feet. Both feet were warm. All pulsations were present in the right lower extremity. The left external iliac pulse was small. The left femoral pulse was absent, and there was no pulse in the left lower extremity. The oscillometer readings were: left calf, 0.5; left ankle, 0.25; right calf, 5; right ankle, 1.5. She was advised to refrain from smoking, to exercise, and to receive intravenous injections of saline solution. She reported by letter in September, 1945, that she was feeling better.

CASE 19 (8053).—A. S., an American gentile woman, was 31 years of age when seen in December, 1945, four months after a mid-thigh amputation of the right lower extremity. She stated that she had started to smoke at the age of 19 years and usually smoked twenty cigarettes a day. Two years later, at the age of 21, she first noticed intermittent claudication, chiefly in the right leg, after walking ten blocks. This condition gradually became worse and she was able to walk only two blocks without stopping. In April, 1941, she had a frostbite. She was admitted to the Greenwich Hospital in Connecticut where a diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking, which she did for two and one-half years, but then she started to smoke again. She noticed immediately that her walking became worse. In November, 1943, she developed tenderness near the nail of the right first toe. She returned to the hospital and an incision was made around the nail, resulting in a deep, tender ulcer with exposure of bone. This continued for nine months. She continued to smoke while in the hospital but stopped smoking in 1944. In December, 1944, the great toe of the right foot became inflamed. She was again treated at the Greenwich Hospital with Depropanex and saline injections, intravenously. In August, 1945, gangrene of the right foot developed and a right mid-thigh amputation was then done.

When she was examined in December, 1945, the general physical examination was essentially negative. She had advanced impairment of circulation in the remaining left lower extremity. There was a well-healed mid-thigh stump. The right radial pulse was absent; the ulnar pulse was present. The left radial pulse was present, but the left ulnar pulse could not be felt. The left popliteal pulse was absent and there was no pulse in the foot. The oscillometer readings were: both wrists, 2.5; left calf, faint; left ankle, very faint. She was last seen in September, 1946. She was wearing an artificial leg and was able to walk one block without stopping. She was receiving injections of 5 per cent sodium chloride solution three times a week.

This is the only woman patient with thromboangiitis obliterans seen by the writer who has had an amputation of a leg.

CASE 20 (8149).—S. R., an American Hebrew woman, 30 years of age, was first seen in January, 1946. In June, 1944, she had had an attack of pain and swelling of the right ankle. In May, 1945, she began to have intermittent claudication in the right leg after walking two blocks. She was studied at The Mount Sinai Hospital at that time. She was married and had one child. She had begun to smoke at the age of 18 years and smoked twenty cigarettes a day. The general examination, including the Kahn test, urinalysis, and blood count, was negative. The basal metabolic rate was −11 per cent. X-ray films of the right foot were negative. There was persistent absence of the right posterior tibial pulse and some reduction in oscillometer readings. Skin tests to tobacco were positive. A diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking but did not do so. About December, 1945, the right third toe became discolored and painful and three weeks later a black spot developed. On examination at this time, the left foot was considerably cooler than the right. Both femoral and both popliteal pulsations were present. The left anterior tibial pulse was present, but there was no other pulse

in either foot. There was an area of gangrene, 1.0 cm. in diameter, on the mesial surface of the tip of the right third toe. The oscillometer readings were: left calf, 5; left ankle, 1.5; right calf, 4; right ankle, 1. Circulation in the upper extremities was normal. She was again advised to stop smoking and received intravenous typhoid injections for relief of pain. Her condition slowly improved, and when she was seen in June, 1946, pain was much less. The same pulses were present, but the oscillometer readings were: left ankle, 2.25; right ankle, 1.5. The gangrenous area on the right third toe had separated and a clean, healing ulcer was present at the tip of the toe. In October, 1946, the ulcer was completely healed and there was no longer any pain.

Although this patient, like several others in this series, had the benefit of an early diagnosis of thromboangiitis obliterans, she failed to heed advice to give up smoking until she developed gangrene of a toe.

CASE 21 (8304).—S. D., an American Hebrew woman 37 years of age, was first seen in March, 1946. For two years she had noticed numbness of the toes of both feet after walking six blocks. Occasionally, she had swelling of the instep. She smoked fifteen cigarettes a day. She was married and had three children. Examination showed a healthy, well-nourished woman. The general physical examination was negative. Circulation in the upper extremities was normal. Both feet were cold. Both femoral and both popliteal pulses were present. There was no pulse in either foot. The oscillometer readings were: left calf, 5; left ankle, 1.5; right calf, 5; right ankle, 1. There was rubor of both feet on dependency and blanching on elevation. She was advised to stop smoking and was encouraged to walk several miles daily. No other treatment was recommended.

This is a typical early case of thromboangiitis obliterans in a woman. If she obeys instructions to avoid tobacco it is unlikely that she will have further trouble with her legs.

CASE 22 (8471).—L. A., an American Hebrew woman 24 years of age, was seen in May, 1946. She gave a history of having had an injury to the right third finger in Septenber, 1943. X-ray films were negative for fracture. The finger continued to be painful and an ulcer developed on the tip; the finger also became gangrenous. There was no improvement after conservative treatment for four months. She was then hospitalized and the terminal digit of the right middle finger was amputated. Some months after this she began to have pain in the left index finger. After an injury to this finger, gangrene developed at the tip and a small part of the finger sloughed away. Since then, the left fifth and the right fourth and fifth fingers had become painful and had developed secretion under the nails. Later, the left fourth finger became similarly affected. Recently, she developed a small ulcer on the left first toe. The patient had begun to smoke at the age of 16 years and smoked about twenty cigarettes daily. Although she was advised to stop, she has never done so for more than a week. The general physical examination showed a well-nourished young woman and was essentially negative. The left thumb was normal. The nail of the left index finger was long and curved and slightly tender to pressure; there was no obvious ulceration or infection. There was a portion of protruding bone at the tip of the left third finger with a surrounding hard crust. The distal joint was ankylosed. There was some swelling of the terminal portion of the left fourth finger with infection beneath the nail. There was a heavy crust at the tip of the left fifth finger. The left second, third, and fifth fingers tapered toward the ends. The distal phalanx of the right third finger was missing; the finger was perfectly healed; there was good motion at the proximal interphalangeal joint. The right thumb was normal. There appeared to be some infection beneath the nails of the fourth and fifth fingers. The tip of the fourth finger was moderately tender. Part of the nail was missing from the right index finger. She was unable to make a complete fist with either hand. All the fingers of the right hand except the thumb were cooler than the fingers of the left hand. Both radial arteries were open; both ulnar arteries were closed. There was a positive Allen test on both sides. The oscillometer readings were: left wrist, 2; right wrist, 2. All pulses were present in the right foot. The left posterior tibial pulse was good. The left anterior tibial and dorsalis pedis pulses were absent. The oscillometer readings were: left ankle, 3; right ankle, 3.5. There was an ulcer mesial to the nail of the left first toe which appeared to be due to the pressure of the sharp edge of the nail. X-ray films of the hand made on three different occasions showed no abnormalities in the tufts of the bones of the terminal phalanges.

A diagnosis of Raynaud's disease had been made by several physicians. However, there were none of the characteristic manifestations to justify this diagnosis. She gave no history of any blanching or other color changes on exposure to cold; she frequently went about without gloves in the winter. Even now, in spite of the ulcers present on many fingers, she still had no complaints of color changes in the fingers on exposure to cold.

CASE 23 (8608).—H. K., an American Hebrew woman 40 years of age, was first seen in June, 1946. For eight months she had had pain in both feet after walking two blocks, worse on the left side. There was no pain at rest. She had been smoking twenty cigarettes a day for two and one-half years. The history was otherwise negative. She was married and had one child. Physical examination showed a well-nourished woman who looked much younger than her age. The examination was essentially negative except for the extremities. Both radial arteries were open. Both ulnar arteries were closed, and the Allen test was positive in both hands. Both femoral and both popliteal pulses were present. All normal pulses were absent in both lower extremities, but there were good peroneal pulses in both feet. The oscillometer readings were: left calf, 5; left ankle, 0.5; right calf, 5; right ankle, 2.5. She was advised to stop smoking and was encouraged to walk several miles each day.

When last seen, in September, 1946, she stated that her feet felt somewhat warmer and that she was able to walk three or four blocks without stopping. However, her circulation remained unchanged and treatment with intravenous injections of 5 per cent saline solution was recommended.

A diagnosis of thromboangiitis obliterans could be made in this patient because of the evidence of impaired circulation in all four extremities, her generally youthful appearance, and the absence of any signs of arteriosclerosis. The late appearance of the disease is explained by the fact that she had started smoking at the age of 37 years.

CASE 24 (8746).—J. A., an American gentile woman 39 years of age, was seen in October, 1946. For two and one-half years she had had attacks of pallor and pain in the left fifth finger. Three weeks previously the left fourth and fifth fingers had turned dark. She had been admitted to a hospital and treated with Dicumarol, niacin, phenobarbital, and intermittent venous occlusion. She was smoking fifty cigarettes daily. There was no complaint of trouble with walking. Physical examination was essentially negative. Circulation in the right hand was normal. The left radial artery was open; the ulnar artery was closed. The Allen test was positive. The left fifth finger was somewhat cooler than the others; it had a glossy, red appearance. The skin of the terminal phalanx was thickened. The finger was tender to firm pressure. All pulsations were present in both feet and were normal in size. The oscillometer readings were: left ankle, 4; right ankle, 3.5. There was some rubor of the toes of both feet. The feet were warm. A diagnosis of thromboangiitis obliterans was made. She was advised to stop smoking, but no other treatment was felt to be necessary.

This is a typical early case of thromboangiitis obliterans with involvement of one upper extremity before any symptoms appeared in the feet.

CASE 25 (8834).—S. P., an American Hebrew women, 31 years of age, was first seen in November, 1946. She gave a history of cramps in the left foot on walking three blocks. The cramps had been present for a year. She had no other complaints. She had begun to smoke at the age of 16 and smoked twenty cigarettes daily. She was married but had no children. Examination showed an overweight young woman whose general physical examination was negative. Both ulnar pulses were absent. Both radial pulses were present. There was marked rubor of the left foot. There was some thickening of the veins on the dorsal surface of the outer side of the left foot. The left femoral pulse was present; the popliteal pulse was absent. There was no pulse in the left foot. All normal pulses were present in the right foot except the dorsalis pedis. The oscillometer readings were: left calf, 0.75; left ankle, faint; right calf, 6; right ankle, 2.5.

This is a typical case of thromboangiitis obliterans in a woman showing involvement of both upper and both lower extremities.

REVIEW OF CASE HISTORIES

Study of the case histories reveals certain facts which require emphasis. The most important finding is that thromboangiitis obliterans in women very frequently involves the hands, and occasionally *begins* in the fingers (Cases 12, 14, 22, and 24) rather than in the feet. In men it is extremely rare for this disease to begin in the upper extremities. In Table I it will be noted that fourteen of the twenty-five cases of women (56 per cent) showed signs of circulatory disease in the upper extremities.

TABLE I. CLINICAL DATA ON TWENTY-FIVE WOMEN WITH THROMBOANGIITIS OBLITERANS

CASE NO.	AGE AT ONSET (YEARS)	NO. OF CIGARETTES SMOKED DAILY	SEVERITY OF INVOLVEMENT*	UPPER EXTREMITY INVOLVEMENT
1	28	20	3 +	No
2	27	15	2 +	Yes
3	28	20	3 +	No
4	36	40	3 +	No
5	34	20	3 +	No
6	30	20	4 +	Yes
7	26	20	3 +	No
8	30	15	4 +	Yes
9	22	40	3 +	No
10	27	20	4 +	No
11	28	20	1 +	No
12	26	20	1 +	Yes
13	29	10	3 +	No
14	29	20	3 +	Yes
15	22	20	3 +	Yes
16	38	20	3 +	Yes
17	21	20	3 +	Yes
18	27	30	4 +	Yes
19	21	20	3 +	Yes
20	28	20	2 +	No
21	35	15	2 +	No
22	21	20	1 +	Yes
23	39	20	2 +	Yes
24	36	50	1 +	Yes
25	30	20	3 +	Yes

*Explanation of degree of circulatory impairment: 4 +: femoral, popliteal, anterior tibial, and posterior tibial arteries closed; 3 +: femoral artery open, popliteal, anterior tibial, and posterior tibial arteries closed; 2 +: femoral and popliteal arteries open, anterior tibial and posterior tibial arteries closed; 1 +: femoral and popliteal arteries and one foot pulse open, one foot pulse closed.

When circulatory disease occurs in the hands of a woman, the differential diagnosis between thromboangiitis obliterans and Raynaud's disease becomes very important. Unless the proper diagnosis is made, treatment is almost certain to be incorrect and unsuccessful. Raynaud's disease is pre-eminently a condition which occurs in women, and involvement of the hands is characteristic. Patients with Raynaud's disease complain of blanching of the fingers on exposure to cold. This is due to spasm of the digital arteries shutting off circulation to the finger tips. Female patients with thromboangiitis obliterans also complain of blanching of the fingers on exposure to cold. This is due to vasoconstriction superim-

posed upon organic disease in the digital vessels. The blanching in Raynaud's disease is likely to involve several fingers, and symmetrical fingers of both hands. The blanching in thromboangiitis obliterans is more likely to involve only one finger of one hand. Pain is not a prominent feature of Raynaud's disease. Patients with this condition complain of tingling during the hyperemic or red phase of the attacks, but between attacks there is usually no pain unless ulceration is present. In contrast, the patient with thromboangiitis obliterans complains of constant pain in the affected finger. This is an important clue to the nature of the illness. On examination, the patient with Raynaud's disease will show equal temperature of all fingers between attacks since it is only during the period of spasm that circulation is temporarily impaired. On the contrary, the patient with thromboangiitis obliterans will show persistent coldness of the involved finger at all times. Finally, examination of the lower extremities will reveal normal arterial circulation in Raynaud's disease, but some pulsations are likely to be absent in patients with thromboangiitis obliterans. If these points are kept in mind it is usually possible to distinguish between the two conditions.

Three of the twenty-five patients (Cases 4, 6, and 17) in this series showed cerebral involvement (12 per cent). The incidence of cerebral involvement in male patients with thromboangiitis obliterans has been less than 1 per cent, and at first glance the higher incidence in women is striking. However, because of the relatively small number of female patients with this disease, this figure cannot be considered significant unless it is confirmed in a much larger series of cases.

It is discouraging to note that women are even more prone to resume smoking and cause recurrence of their trouble than are men. Emotional disturbances, the tendency to put on weight, or recurrence of habit are given as the usual reasons. In such instances, when the patient returns, it is usually found that the circulation is much worse than when she was first seen, and the long course of treatment necessary to improve it must be resumed.

The opportunity to study many additional cases of thromboangiitis obliterans in women has thrown no further light upon the relative immunity of this sex to the disease. The women who developed thromboangiitis obliterans showed no changes in menstruation, child bearing, or physical characteristics to distinguish them from other members of the female sex. Dr. Robert T. Frank was kind enough to study the excretion of estrogens in all the urine passed for one month in two patients in this series (Cases 8 and 10). He was unable to detect any abnormalities in this respect.[12] A family history of thromboangiitis obliterans was searched for, but was not found in any of the twenty-five women in this series. Unless future experience shows a much greater incidence of the disease in women, it may be necessary to accept as an explanation that women do not frequently inherit the specific sensitivity to tobacco which is apparently needed to make possible the development of thromboangiitis obliterans.

All of the women in this series with thromboangiitis obliterans were habitual smokers. Progression of the disease was regularly associated with the continued or resumed use of tobacco. All patients restored to good health who have refrained from smoking have remained in excellent condition. Thromboangiitis obliterans in women, as in men, is due to the use of tobacco by persons sensitive

to this substance. The most essential part of treatment is to make sure that these patients stop smoking permanently.

Since there have been only twenty-five instances of thromboangiitis obliterans in women in over 1,600 cases of this disease seen by the writer, it is still a rare condition in the female sex. However, the occurrence of occlusive vascular disease in young women must be regarded as manifestations of thromboangiitis obliterans unless there is another obvious cause.

SUMMARY

Twenty-five cases of thromboangiitis obliterans in women are presented. The greater tendency for the disease to manifest itself in the hands of women is pointed out. The differential diagnosis between Raynaud's disease and thromboangiitis obliterans is discussed. The etiological relationship of thromboangiitis obliterans to the use of tobacco is again demonstrated.

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Clinical Reports

A CASE OF PARADOXICAL EMBOLISM

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PARADOXICAL embolism, while not rare, is relatively uncommon, as evidenced by the fact that only twelve references have been found in a search through the available literature for the period 1921 to 1945. It is also of particular interest at this time because of the extensive studies being carried on in many centers in connection with thromboembolic phenomena.

Patency of the foramen ovale is not infrequently found when it is searched for diligently. Thompson and Evans[1] reported studies conducted along these lines on 1,100 consecutive autopsies, and reported varying degrees of patency in 35 per cent of these cases. In 29 per cent, the opening in the foramen ovale would admit a probe, and in 6 per cent, it was sufficient to admit a pencil.

From this it is readily reasoned that some other factor might be operative in causing embolic material to pass from the right side of the heart directly into the arterial circulation; otherwise, the condition should be encountered much more often than it is. With these considerations in mind, the following report of a case was felt to be justified.

CASE REPORT

W. B., a 69-year-old white man, had a transurethral prostatectomy for a benign prostatic hypertrophy on Sept. 20, 1946, in the Royal Alexandra Hospital. His postoperative course was entirely satisfactory in that his temperature was not unduly elevated and subsided to normal by the fifth day. However, on the eighth day he experienced slight pain in the left calf, and when the chart was reviewed, it was noted that he had a temperature elevation amounting to 101.4°F. on that day. There was also some indication of slight pitting edema in the left leg.

He was kept at complete rest and when he received his discharge from the attending surgeon on Oct. 11, 1946, his condition was apparently quiescent. However, he had to be readmitted as an emergency within twelve hours of his leaving the hospital because of a secondary hemorrhage into his bladder.

This was followed by a febrile episode lasting about five days, during which time he was given local treatment in the form of bladder irrigations and general treatment by the administration of penicillin intramuscularly. His recovery from this was such that he was permitted to be up and about in six days' time.

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About noon on October 19, shortly after returning from the lavatory, he was found sitting on the edge of his bed, dyspenic, cyanosed, and obviously in an advanced state of collapse. He was only able to indicate intense upper abdominal pain.

A tentative diagnosis of massive pulmonary embolism was made. Measures such as the administration of intravenous heparin and papaverine were instituted at once, along with oxygen administration.

An electrocardiogram taken subsequently (Fig. 1) lent further weight to the diagnosis, as there was definite indication of acute cor pulmonale. A portable roentgenogram of the chest showed, "patchy consolidation involving both lungs, which, in view of clinical findings, could be due to massive, bilateral pulmonary embolism."

The patient lapsed into a comatose state, and he remained extremely cyanosed in spite of continuous administration of oxygen by mask. In contradistinction to what is usually noted under such circumstances, his pulse was not excessively elevated and his blood pressure did not drop as was anticipated.

The patient remained in this state for approximately fifty-one hours, when death finally took place. An electrocardiogram taken two hours before death is shown in Fig. 2.

The post-mortem examination was made eighteen hours after death by one of us (C. R.). When the thorax was opened, it was noted that both lungs were contracted to about one-half the size usually found under such circumstances. They were of a dark, livid color and exhibited almost a total lack of aeration. It seemed extremely remarkable that this patient had been able to live so long when so little pulmonic tissue was capable of its respiratory function.

The majority of the branches of the pulmonary artery were occluded with what appeared grossly to be recent ante-mortem thrombus. This, on section, was seen to be composed of laminated masses of platelets and red blood cells. The outlines of the red blood cells were clearly visible everywhere, except at the periphery of the clot where slight red cell degeneration was present and only "ghosts" of red cells were seen. There was also slight round cell and polymorphonuclear infiltration in this area. One of the larger branches of the pulmonary artery supplying the right lower lobe was found to be occluded by what appeared to be a somewhat older thrombus. This, on section, showed the typical appearance of early organizing thrombus. Red cell outlines were only occasionally visible in a mass of greyish amorphous-appearing material which showed marked infiltration with round cells, phagocytes containing blood pigment granules, and a few polymorphonuclear leucocytes. The margins of this thrombus showed infiltration with young fibroblasts. This latter finding suggested that a recent previous embolism had taken place. While the right auricle was moderately distended, the distention was not near that usually anticipated under such conditions.

On further examination of the abdominal organs, both kidneys showed recent and older areas of infarction, and both renal arteries, on careful examination, were found to contain fresh emboli. This was rather perplexing in view of the fact that a preliminary examination of the heart did not reveal any obvious cause, such as vegetations or mural thrombi, in the chambers of the left side of the heart.

A careful examination of the foramen ovale revealed an opening which was covered by a vestige of the septum primum acting as a valve flap. The free edge of this structure protruded into the lumen of the left atrium in such a way that blood could flow from the right atrium to the left, but it could be closed by any reversal of this process. The aperture covered by the valve flap would readily admit a lead pencil (Fig. 3).

Further examination revealed the presence of thrombophlebitis, involving the left deep femoral vein. In addition to this, extensive thromboses were found in the venous plexus about the prostatic bed. It seemed more likely that the massive terminal pulmonary and renal infarction must have been due to embolism secondary to the femoral thrombophlebitis.

The presence of varying degrees of organization and resolution found in the infarcted areas in both the lungs and kidneys indicated that showers of emboli must have been released some time prior to the massive terminal episode.

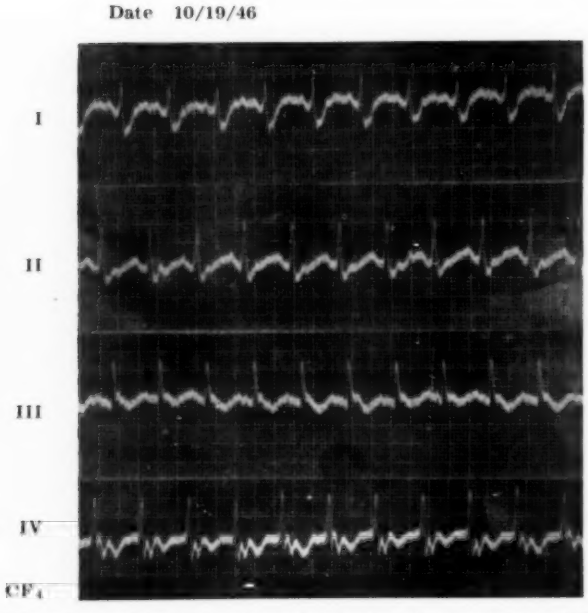

Fig. 1.—Electrocardiogram taken about three hours after the onset of the pulmonary embolism. It shows a sinus tachycardia with a rate of 124 per minute, marked S waves in Leads I and II. There are inverted T waves in limb Lead III and CF_4. In addition to this, there is a slight elevation of the S-T interval in limb Lead III.

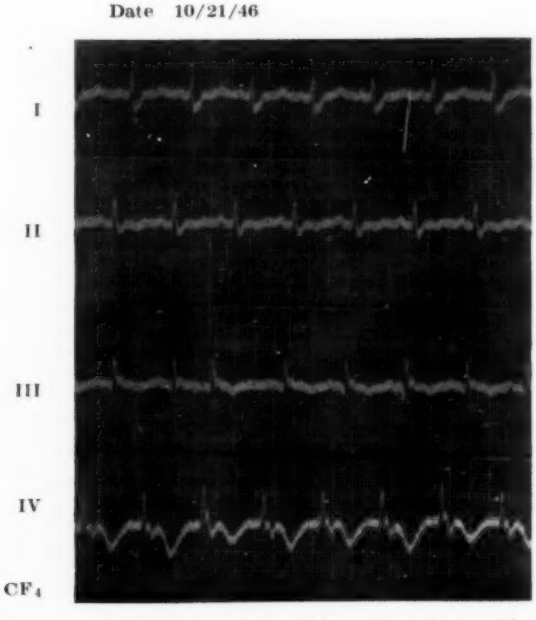

Fig. 2.—Tracing taken approximately two hours before the patient suddenly expired. The rate is 116. There is a sinus tachycardia with a rate of 116 per minute and occasional premature auricular contraction. S waves are still present in Leads I and II, but not to as marked an extent as in the preceding tracing. The T waves are negative in Lead III. There is a marked negative T wave in CF_4. The same slight elevation of the $S\text{-}T_2$ persists without any reciprocal change seen in $S\text{-}T_1$.

Fig. 3.—A view of the foramen ovale from the right auricular side showing closure of the valve flap by pressure from the left atrial side, simulating a condition normally found where the patent foramen ovale is protected by a valve flap derived from a vestige of the septum primum. There is no increased right atrial pressure present. The arrow points to closed valve flap covering the patency in the foramen ovale.

DISCUSSION

Apart from the fact that there was a patent foramen ovale in this case, two other interesting features deserve recognition and analysis: The first is the probability that pulmonary embolism was a precipitating factor in forcing embolic matter through the foramen; the second is that this individual lived much longer than would have been anticipated after having sustained such a massive pulmonary embolism.

The first of these considerations is not an original observation, as Wittig,[2] in 1927, noted that 50 per cent of the cases of paradoxical embolism were associated with preceding pulmonary embolism. This is readily explained by the sudden rise of pressure in the right atrium, as a result of obstruction in the pulmonary artery and its branches, which is presumably great enough to force open the valve flap of the foramen ovale. In this way, embolic material could be forced directly into the left atrium and thus pass into the systemic circulation. It is quite apparent that such a mechanism must have been operative here.

Visscher[3] has established the important role which the Thebesian system of veins plays in the return flow of the coronary blood in the right atrium and ventricle. He has also indicated how this renders the right side of the heart particularly vulnerable to increased intra-atrial and intraventricular pressure. It is reasonable to assume that in this case the patent foramen ovale acted as a safety valve. In this way, the function of the Thebesian system was not disturbed as it might have been if no opening existed in the intra-atrial septum.

In the average case of massive pulmonary embolism, Currens and Barnes[4] have expressed their belief that one of the main causes of death is impairment of the coronary circulation to the right heart. This is due to the rise of pressure in the right atrium which decreases the pressure gradient in the coronary circulation.

Thompson and Evans[1] comment on the fact that one of their patients survived pulmonary embolism for forty-eight hours in the presence of a patent foramen ovale. They did not elaborate on this, however.

Fig. 4.—A view of the foramen ovale from the right side showing opening of the valve flap by pressure from the right atrial side, simulating the condition arising in the presence of increased right atrial pressure. A medium-sized pair of thumb forceps is inserted in the opening, showing the degree of patency of the foramen ovale.

In this case, it appeared rather remarkable that life could have been maintained for fifty-one hours when so little functioning lung tissue remained. The evidence accumulated in this case would seem to indicate that patency of the foramen ovale, under these conditions, might serve to increase the pressure gradient in the coronary circulation of the right side of the heart. This would seem to be a reasonable explanation as to why this individual lived as long as he did after such massive pulmonary embolism.

SUMMARY

1. A case of paradoxical embolism is presented.
2. Its relationship to pulmonary embolism is indicated.
3. An explanation for the unusual prolongation of life in this case is suggested.

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EXTREME BRADYCARDIA

Report of a Case Exhibiting a Ventricular Rate of Less Than Twelve per Minute

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THE recognition and description of interference in auriculoventricular conduction is not a matter of recent observation, for Galen in 130 A.D. commented on this condition.[1] Heart block of some type or degree is a common occurrence. A sustained rate below 15 beats per minute, however, rarely has been observed, only three such cases having been reported in the past two decades.[2,3,4] Of these, only Ruggiero,[4] in 1937, recorded the bradycardia electrocardiographically. The patient was a 53-year-old white man whose ventricular rate shortly prior to death varied between 10.8 and 20 beats per minute, and whose auricular rate ranged between 79 and 88 per minute.

It is our purpose to report a case in which heart block produced an unusually slow cardiac rate associated with the Stokes-Adams syndrome. As far as we have been able to discover, this patient exhibited the slowest ventricular rate ever recorded by the electrocardiograph in man.

CASE REPORT

B. D., a 69-year-old Russian-born white man, was admitted to the private service of one of us (J. C. D.) on March 16, 1947, with the chief complaint of shortness of breath which had existed since Feb. 25, 1947, at which time he began to note rather severe dyspnea on exertion followed by regular attacks of paroxysmal nocturnal dyspnea. On March 6, 1947, he was aware of considerable ankle edema. The dyspnea grew progressively worse, and the patient was referred to the Jewish Hospital for study.

At the initial examination the patient appeared to be somewhat younger than his stated age. His temperature was 98° F.; the pulse and respiratory rates were 36 and 24 per minute, respectively. The systolic blood pressure was greater than 260 mm. Hg, the diastolic pressure, 90. There was slight weakness of the right side of the face which the patient claimed had been present for many years. The neck veins were markedly distended. On examination of the chest, fremitus was decreased, the percussion note impaired, and breath sounds diminished over the lower portion of the right hemithorax, posteriorly. The heart was moderately enlarged, the apex beat being palpated about 2.0 cm. to the left of the mid-clavicular line. The ventricular rate was very slow, 36 per minute, and the rhythm was regular. The systolic sounds were of good quality; no murmurs were heard. The second pulmonic sound was greater than the second aortic sound. The abdomen was flat and there was no tenderness. The liver was palpated about 2.0 cm. below the costal margin. There was edema of the arms, thighs, legs, and ankles.

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The original examination of the urine showed a pH of 7.5, specific gravity of 1.021, and 4 plus albumin. Examination of the blood showed 15.9 Gm. of hemoglobin, 5,410,000 erythrocytes, 14,450 white blood cells, and a normal differential count. An electrocardiogram on admission confirmed the presence of a marked bradycardia (34 per minute) and revealed a 2 : 1, and sometimes a complete heart block, as well as definite evidence of a healed anterior myocardial infarction.

Because of the evidence of congestive heart failure and the marked hypertension, 200 c.c. of blood was removed rapidly. At 12:30 A. M. on the day of admission the patient was seen in a typical attack of nocturnal dyspnea. His color was grey, dyspnea was severe, and the thorax was filled with loud asthmatoid wheezes. Prompt relief followed the use of aminophyllin, intravenously, and morphine sulfate and atropine sulfate, subcutaneously. Later that morning digitalization (digitoxin) was begun and general supportive therapy continued. On the third hospital day 800 c.c. of a clear, yellow transudate was removed from the right hemithorax.

A Fishberg urinary concentration test revealed a fixed specific gravity, the urine containing many granular and hyaline casts. An electrocardiogram revealed complete heart block with a ventricular rate of 28 and an auricular rate of 60 per minute. In addition, there was evidence of block of the right bundle branch. The condition improved and on March 30 the patient was breathing comfortably without oxygen and was allowed to sit on the side of the bed. Cardiac auscultation revealed a rate of 30 per minute. The sounds were still of good quality and in diastole a third distant sound was heard, which was believed to be produced by the auricular contraction. An attempt to speed the ventricular rate by means of the oral administration of atropine sulfate, grain 1/200 three times per day, was unsuccessful.

On April 1, 1947, at 10 A. M., the patient vomited, had mild twitching of the face, and became apneic and cyanotic. He was ashen grey and perspiring profusely, but still well oriented and had no motor or sensory paralyses. Oxygen therapy was reinstituted and caffeine with sodium benzoate was given subcutaneously. Three times in the following six hours, when the oxygen mask was removed, the patient exhibited the following phenomena: the face became florid, the eyes rolled upward and outward, there were twitchings of the facial muscles, a slight pinkish froth was seen at the mouth, and the respirations became weak and shallow. During the last of these three attacks, it was noted that the blood pressure had dropped to 170, systolic, and 60 to 70, diastolic, and that the pulse rate at the apex, as well as in the peripheral vessels, was 14 to 16 per minute. An electrocardiogram showed a ventricular rate of 12.5 to 13 per minute with an auricular rate of 50 per minute, left axis deviation, and a prolonged QRS complex (0.14 second) suggesting left bundle branch block as well as complete A-V heart block (Fig. 1,*A*).

The digitoxin was discontinued after a total of 2.4 mg. had been given in a period of fifteen days. Caffeine with sodium benzoate, grains 40; strychnine sulfate, grain 1/10; and ephedrin sulfate, grains 2¼ (grain 3/8 every fourth hour for six doses) were administered in a period of twenty-four hours. Of these, only ephedrin definitely produced acceleration of the ventricular rate.

The following morning the patient appeared to be improved, the cardiac rate having returned to 36 per minute. On only one occasion did he exhibit any further manifestations of the Stokes-Adams syndrome. An electrocardiogram taken late that afternoon revealed a ventricular rate of 34 per minute, an auricular rate varying between 62 and 85 per minute, and a prolonged QRS complex (0.12 second) with a suggestion of right bundle branch block (Fig. 1,*B*).

At 8 A. M., April 4, the patient became semistuporous, and when he was seen, the radial and apical pulses were approximately 8 per minute. A single lead (CR_4) of an electrocardiographic tracing taken at 10 A. M. showed a rate between 11 and 12 per minute (Fig. 1,*C*). Convulsive seizures became more frequent. At 12 noon, in spite of therapy, the radial and apical rates were between 8 and 10 per minute. An electrocardiogram taken between 12:20 and 12:40 revealed a ventricular rate averaging 9.8 per minute and an auricular rate of 110 per minute (Fig. 1,*D*). Five minutes later, with the electrocardiograph still running, in spite of an intracardiac injection of adrenalin, the heart action ceased and the patient was pronounced dead (Fig. 1,*E*).

Post-Mortem Examination.—Post-mortem examination was performed approximately four hours after death by Dr. Leonard L. Malamut. The pleurae were obliterated by old, dense adhesions. There was a small, loculated effusion in the interlobar fissure on the right. The vessels

showed some atherosclerosis, especially the abdominal aorta. There were small cysts approximately 5 cm. in diameter containing clear fluid scattered throughout the parenchyma of both kidneys. The remainder of the organs, with the exception of the heart, showed no changes of any importance.

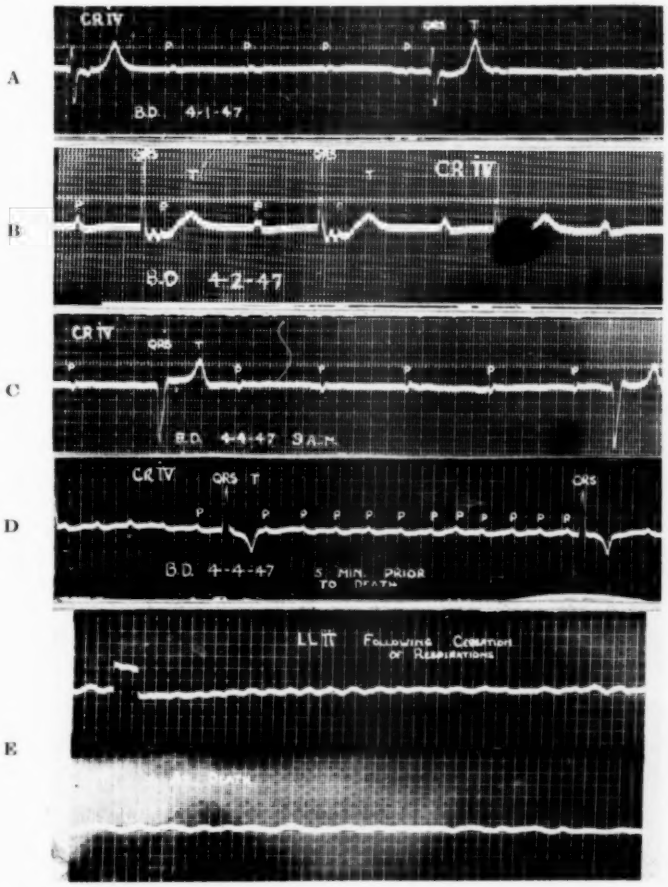

Fig. 1.—A series of electrocardiograms taken *A*, three days before death (ventricular rate, 12.5, auricular rate, 50); *B*, two days before death, af er oral administration of ephedrin sulfate (ventricular rate, 34); *C*, three hours before death (ventricular rate, 11.5); *D*, five minutes before death (ventricular rate, 9.8); *E*, following cessation of respirations.

All tracings are lead CR_4; other leads are omitted. *D* and *E* taken with paper running at higher speed.

In situ, the heart appeared to be moderately enlarged. It weighed 420 grams. The color and tone of the myocardium were exceptionally good, and there was no gross evidence of any involvement of the septum or wall of the left ventricle. The tricuspid and mitral valves were normal for the age of the patient, but there was slight fibrosis of the valvular rings. The pulmonic valve was normal, and the cusps of the aortic valve showed a minimal amount of fusion. The endocardium appeared normal throughout and there were no gross abnormalities of the auriculoventricular node or of the bundle of His. Both coronary arteries showed a moderate amount of atherosclerosis for the first 5 to 6 cm., but the lumina remained completely patent to the smallest ramifications. A small accessory coronary vessel arose at the mouth of the right coronary artery from the anterior sinus of Valsalva.

Microscopic examination of the heart muscle, per se, revealed no definite pathologic changes except some hypertrophy of the wall of the left ventricle. Special serial sections were made of the bundle of His and stained by hematoxylin and eosin as well as by the Mallory trichrome technique. In an area just below the membranous septum, distal to the bifurcation of the bundle, there was found a plaque of calcific deposit with a maximum diameter of 0.5 mm. (Fig. 2), around which there was a large amount of collagenous material. In the anterior portion of one section this calcification involved chiefly the right bundle branch, and in the posterior portion, the left bundle branch. As the sections progressed it became obvious that most of both bundles were involved, as evidenced by the increase in vacuolization of the cells comprising the Purkinje fibers, and finally, almost complete necrosis of these cells. A section through the A-V node also revealed small calcific deposits involving some cells of the conduction system (Fig. 3).

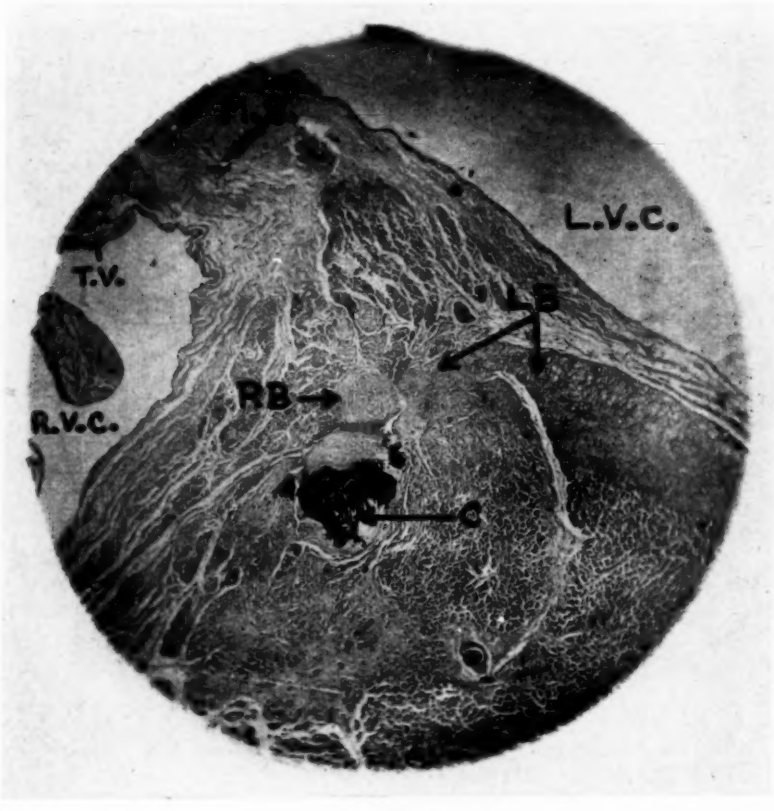

Fig. 2.—Section through interventricular septum showing large calcific plaque (C) involving most of the right bundle (*R.B.*) and a very small portion of the left bundle (*L.B*). *T.V.* designates the tricuspid valve; *R.V.C.*, the right ventricular cavity; *L.V.C.*, the left ventricular cavity; *M.S.*, the membraneous portion of the interventricular septum. × 37.5.

DISCUSSION

The exact etiology of the complete heart block in this patient was in doubt until careful histologic examination was made of serial sections of the conduction system. No gross occlusive process was found in any of the coronary vessels; indeed, the lumina of these vessels were unusually large and their endothelial

surfaces surprisingly free of atherosclerosis, considering the patient's age. Perhaps the adequacy of the blood supply to the heart muscle itself accounted for its ability to maintain the minute cardiac output at a volume which was consonant with life.

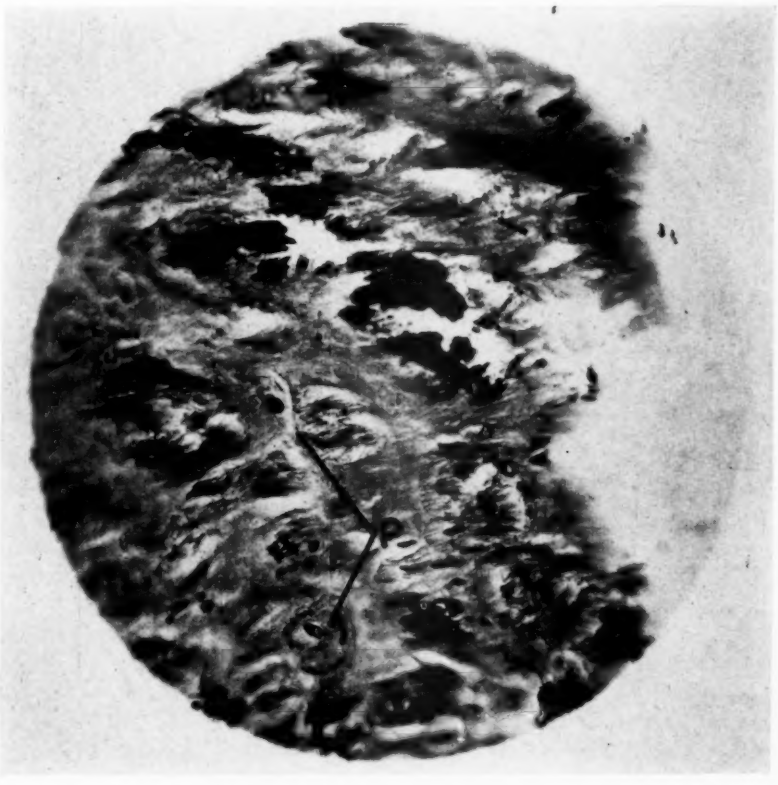

Fig. 3.—Section from area of A-V node exhibiting small calcific areas (heavily stained portion) and paucity of normal cells of the conduction system (*P*). × 400.

The many causes of heart block are well known. Arteriosclerosis, predominant among these, accounted for 62 per cent of Willius' series of thirty-seven cases.[5] Intrinsic heart disease, endocrine disturbances, digitalis, malignancies, chemical poisoning, anaphylaxis, and various infections have been found at one time or another to be the underlying pathologic condition in heart block. Notwithstanding the diversity of etiology, pathologic changes in complete heart block remain obscure in about 10 per cent of cases. In the case reported, calcific deposits, so situated that they could have been partially or wholly responsible for the conduction defect present, furnished an adequate pathologic explanation of the A-V heart block.

Of all the methods of treatment described, including the use of strychnine, atropine, barium chloride, and ephedrin sulfate, the last of these was the only one which seemed to afford some temporary relief to our patient.

SUMMARY

1. A patient with complete heart block whose ventricular rate during the last twelve hours of his life varied from 12.5 to 9.8 beats per minute has been presented.

2. The probable causative pathologic factor in this case was shown to be calcific deposits involving the A-V node and the right and left branches of the bundle of His.

3. It appeared that ephedrin was a useful drug in increasing the ventricular rate and in lessening the frequency of the Stokes-Adams syndrome.

4. This is apparently the slowest sustained heart rate recorded electrocardiographically in man.

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Abstracts and Reviews

Selected Abstracts

Schmidt, E. C. H.: Virus Myocarditis. Pathologic and Experimental Studies. Am. J. Path. **24**:97 (Jan.), 1948.

A virus isolated in 1945 by Helwig and Schmidt from the myocardial lesions of anthropoid apes dying from interstitial myocarditis was found consistently to cause myocardial lesions in mice.

Three apes died, two very suddenly, after exposure to many human visitors. The pathology was strikingly the same in all. A virus was cultured after inoculation of ground spleen into mice. The hearts in all three apes were markedly dilated and on section showed greyish semi-softened areas. Bilateral hydrothorax and a marked hemorrhagic pulmonary edema indicated both subacute and acute congestive failure. Microscopic examination showed extensive necrosis and diffuse round-cell infiltration. Fragmentation and loss of myocardial fibrils was accompanied by inflammatory infiltration of mononuclear and polymorphonuclear cells.

The etiological agent was not looked for in one of these cases of virus myocarditis; it was not found in another case; but in one case the pleural fluid and a splenic extract caused fatal paralysis of the hindquarters in a group of ten mice. Various visceral extracts from these ten mice caused, in turn, a frequently fatal paralysis in a second group of ten mice. Extracts of viscera from this batch of mice and the original fluids were inoculated into other mice, and ten successful mouse passages were made before loss of potency occurred. The mice so inoculated showed a characteristic paralysis on the fourth day, and most of them died on the seventh to the tenth day.

The cardiac lesions in these mice consisted essentially of focal necrosis of the myocardium with monocytic infiltration of the surrounding areas. Interstitial edema and diffuse interstitial cellular infiltration, both monocytic and polymorphonuclear, appeared throughout the myocardium. In those animals surviving until the twelfth day, calcification of the necrotic foci was noted, and after twenty days, this calcification plus fibroblastic replacement were the only remnants of the myocardial disease.

Guinea pigs, to a large degree, and rabbits, to a lesser degree, showed the same myocardial changes in response to inoculation of this virus.

Control animals failed to show any cardiac lesion similar to this type of virus myocarditis. Likewise, sera from patients suffering from rheumatic fever and influenza did not produce lesions of interstitial myocarditis in mice. Mice that had been placed as controls in the same cages as the inoculated animals did not contract the disease.

Intravenous, intraperitoneal, and subcutaneous inoculation, using visceral extracts in acitic fluid-saline suspension, were dependable for the production of the specific myocarditis. Sera of mice that had recovered from the paralysis, when combined in the same inoculum with potent visceral extracts, nullified the action of the latter, thus exhibiting a true antibody action.

While the myocardial lesion of "anthropoid virus disease" duplicates to a remarkable degree human myocarditis associated with various types of virus disease, the authors are reluctant to identify it with human pathology because of their inability to identify this virus with any of the known viruses; also because of the apparent freedom from infection shown by laboratory workers who handled the sick apes.

GOULEY.

Scheinker, I. M.: Alterations of Cerebral Capillaries in the Early Stage of Arterial Hypertension. Am. J. Path. **24**:211 (Jan.), 1948.

Scheinker, continuing his previous studies on the association of arterial hypertension with cerebral vascular disease, describes in this report the early stage of cerebral vascular degeneration with reference especially to changes in the cerebral capillaries. The study was based on findings in six fatal cases of arterial hypertension in which death occurred one to two years after the onset of the disease. However, only two cases are reported in detail.

The first case showed characteristic arteriolosclerosis featured by petechial hemorrhages in the pleura and kidneys. The vessels of the circle of Willis showed a definite arteriosclerosis. There was a small pontine hemorrhage and, in addition, a diffuse swelling of the midbrain with loss of demarcation between gray and white matter.

Microscopically, the important vascular changes were found to be in the capillaries. They exhibited a uniform pathologic process, showing in combination extreme cellular thickening with degenerative alterations of their walls. The thickening was due to a fibroblastic proliferation of the adventitia and hyperplasia of the lining endothelium. Also, there was a pericapillary increase of glial nuclei due to glial hyperplasia in the surrounding nervous tissue. The degenerative changes consisted of a homogeneous thickening of the wall with narrowing and almost complete obliteration of the lumen. Some of these tiny vessels were converted into structureless hyalinized nodules surrounded by glial hyperplasia. The arterioles showed only a moderate degree of thickening and hyalinization. The cerebral veins, however, showed definite changes, there being marked distention of these vessels and degeneration of their walls, even in branches remote from the area of brain hemorrhage. The degeneration of the venous wall also consisted of a structureless, homogeneous, apparently hyaline infiltration. The white matter showed marked increase of fluid content. The perivascular spaces were prominently distended throughout. Scheinker describes the venous changes as those of vasoparalysis.

The second case was that of a patient who died during the course of a Smithwick operation. This case, like the first, showed arteriolonephrosclerosis. Sections throughout the midbrain revealed diffuse swelling of the tegmen of the pons, with almost complete obliteration of lumen of the fourth ventricle.

Again, the striking histologic findings were confined to the capillaries, which showed fibroblastic proliferation of the adventitia and hyperplastic thickening of the lining of the endothelium. Also, aside from the endothelial change, a structureless hyaline thickening of the vessel wall was noted, with narrowing or complete obliteration of the vascular lumen. On the other hand, the arterioles were only slightly affected.

This report points out that an important capillary degeneration constitutes, at least in some cases, the earliest and most accelerated type of vascular change in malignant hypertension. Although the two cases described showed characteristic renal vascular changes, Scheinker feels that in the entire group no direct parallelism could be established between the renal and cerebral developments. In some cases the cerebral vascular changes were clearly predominant.

GOULEY.

Prinzmetal, M., Ornitz, E. M., Simkin, B., and Bergman, H. C.: Arterio-venous Anastomoses in Liver, Spleen and Lungs. Am. J. Physiol. **152**:48 (Jan.), 1948.

Glass spheres ranging in diameter from 10 to 440 μ were injected into afferrent vessels of liver, spleen, and lungs of anesthetized rabbits, cats, and dogs. The spheres were recovered from the venous circulation of all organs. This demonstrates the presence of direct arteriovenous communications because the diameter of the glass spheres definitely exceeded that of capillaries. The results are similar to those reported by the authors for the heart and kidneys and suggest that such routes may be available in all organs. The physiologic significance of such short circuits remains unknown.

HECHT.

Mullick, D. N., Alfredson, B. V., and Reineke, E. P.: Influence of Thyroid Status on the Electrocardiogram and Certain Blood Constituents of the Sheep. Am. J. Physiol. **152**:100 (Jan.), 1948.

The normal electrocardiogram of nine sheep (Lead II) reveals an average heart rate of 112 (88 to 142) per second, a P-R interval of 0.102 (0.08 to 0.14) second, QRS of 0.038 (0.02 to 0.04) second, and a Q-T interval of 0.271 (0.22 to 0.32) second. Bazzett's K value measured 0.367.

Thyroidectomy resulted in a decrease in heart rate and flattening of T which readily reverted to normal upon administration of thyroprotein (1 to 2 mg. per 45 kilograms of body weight). Thiouracil administration resulted in a moderate decrease of heart rate and a paradoxical increase in the height of the T wave. Serum fat levels (Allan) changed little following thyroidectomy and thyroprotein administration. They rose sharply upon administration of thiouracil. No changes could be demonstrated at any time in blood hemoglobin content, serum protein, calcium, phosphorus, or magnesium.

HECHT.

Taylor, H. L., Henschel, A., and Keys, A.: Cardiovascular Response to Posture and the Problem of Faintness and Syncope in the Semi-starved Individual. Am. J. Physiol. **152**:141 (Jan.), 1948.

Thirty-one men were kept on a controlled regimen of activity for six months on a diet of 1,058 calories. This resulted in semistarvation similar to that induced by dietary restrictions of civilian populations in Western Europe during World War II. The subjects lost 24 per cent of their body weight. The cardiovascular effects of posture were studied by the use of a tilting table. Pulse rate, blood pressure, and pulse pressure were reduced in both the horizontal and tilted position. The increase in heart rate and fall in pressure observed as the result of tilting during the control period were found to remain unaltered during the semistarvation period. In the control period four men fainted during ten minutes of tilting. All four withstood ten minutes of tilting during the starvation period. Faintness and dizziness upon arising or unassociated with postural changes were almost universal complaints during the experimental period. It appears that such subjective sensations, together with "blackouts" and "light headedness" during such states, cannot be ascribed to circulatory incompetence.

HECHT.

Roth, G. M., and Sheard, C. H.: Maintenance of Vasodilation of the Extremities of Normal Individuals for a Prolonged Period by the Ingestion of Two to Four Substantial Meals in Close Succession. Am. J. Physiol. **152**:183 (Jan.), 1948.

It was demonstrated in twenty-four normal persons (fifty-two observations) that the rise in skin temperatures of the extremities was greater and could be maintained for about one hour longer after the ingestion of three meals than after one or two meals. An additional two hours of vasodilation were obtained after the ingestion of four meals of 500 to 800 calories taken at two-hour intervals. The rate of sweating and the initial basal metabolic rate obviously modulated the results obtained.

HECHT.

Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions. Ann. Int. Med. **28**:1 (Jan.), 1948.

The original view of the author was that the coexisting endocardial, vascular, serosal, and joint involvement of acute lupus erythematosus must be the manifestation of a primary injury of the endothelial cells and that the disease could be explained as the result of the action of an endotheliotropic injurious factor. Since then, the author has been able to show the presence of a widespread alteration of the connective tissue as well as the endothelium in this disorder. This connective tissue disturbance affects the heart, serous membranes, vasculature, lymph nodes, skin, and mediastinal and retroperitoneal areas. The morbid process becomes manifest in focal fibrinoid metamorphosis of the collagenous fibers, resulting occasionally in fragmentation of these

elements and in swelling and increased density of the interfibrillar homogeneous ground substance which normally is almost invisible. Such foci are more or less heavily infiltrated by polymorphonuclear leucocytes and lymphocytes. The fixed connective tissue cells, fibroblasts, and histiocytes, while increased in number, almost invariably show evidence of decay, such as pyknosis and nuclear fragmentation. The alteration of the glomerular capillaries (wire loops and focal necrosis) is conspicuous in acute lupus erythematosus. Another microsocopic feature present with conspicuous frequency was sclerosis of collagen fibers around the follicular arteries of the spleen. This lesion also reflects a fundamental alteration of the connective tissue though of a nature different from fibrinoid metamorphosis.

The author believes that acute lupus erythematosus is defined anatomically as a disease characterized by a fundamental alteration of the collagenous portion of the connective tissues. In this respect, acute lupus erythematosus shares a common element with generalized scleroderma, rheumatic fever, and even periarteritis nodosa. The author, however, is unwilling to accept a common pathogenesis for this entire group of diseases. He devotes a large portion of the paper to a consideration of the possible causes for such tissue alterations in acute lupus erythematosus and to speculation concerning the fundamental physicochemical disturbance responsible for the changes in the structure of the "ground substance." The role of allergy in the causation of the lesions of disseminated lupus erythematosus is not considered an important one by the author.

WENDKOS.

Humphreys, E. M.: The Cardiac Lesions of Acute Disseminated Lupus Erythematosus. Ann. Int. Med. **28**:12 (Jan.), 1948.

The cardiac lesions in twenty-one authentic cases of acute disseminated lupus erythematosus are analyzed. Endocardial lesions were found in twelve cases. Save for the bulkier lesions affecting two, three, or four valves (observed in seven cases), endocardial lesions were easier to recognize in microscopic sections than they were grossly.

Some focal myocarditis was encountered in most of the twenty-one cases. More significant were: the fine scars, like those of small infarcts; the increased density of collagen along many or most of the intermuscular septa; the thickened small arteries. Myocardial lesions of these types were found beneath the more extensive mural vegetations or near partially or completely occluded arteries. Also there were acute exudative reactions, not easily interpreted. Fresh fibrinoid necrosis of collagen or of vessel walls was easily demonstrable in the more severe cases. In a considerable number of hearts, there was marked loosening of the fibrous substance, producing an edematous appearance not unlike that seen in the beriberi heart. In several, severe fatty degeneration of myocardial fibers was noted. In a number of patients, there were no changes other than interstitial edema, atrophy of fatty tissue, and the presence of dense collagen and a few round cells near the epicardial surface.

In nine cases a serofibrinous pericarditis was present, and in five of these (all with nephritis), there were effusions of 600 to 950 cubic centimeters. In six cases the pleural space was obliterated by loose gelatinous fibrous adhesions. Within these adhesions there were foci of fresh necrosis or of fibrinous and cellular exudation.

In proportion to the wasted state of the bodies of these patients, the cardiac weights were usually normal or slightly increased. In the patients who had nephritis for a sufficient period, weights of 350 to 450 grams were observed. The larger hearts were found in patients whose nephritic symptoms had been present long enough for hypertension to develop.

WENDKOS.

Massey, F. C., and Walker, W. J.: Complete Atrioventricular Block in Diphtheritic Myocarditis. Arch. Int. Med. **81**:9 (Jan.), 1948.

A detailed analysis is made of a complex arrhythmia with complete atrioventricular block and a progressively decreasing ventricular rate occurring in a case of hypertoxic tonsillopharyngeal diphtheria in a 17-year-old white boy. Serial electrocardiograms reflected directly the lesions produced by the disease as observed at autopsy. The fact that the atrial musculature was less

severely impaired than the ventricular accounted for the progressively diminishing ventricular rate despite a relatively constant atrial rate. The serious impairment of the conducting system was the prime basis for the advent of complete heart block and prior intraventricular block. The major microscopic pathology was extensive myocarditis with edema and notable degenerative changes. Occasional cellular accumulations in the periatrioventricular nodal region was so dense that it simulated abscess formation.

BERNSTEIN.

Hendry, W. G.: Superior Mesenteric Arterial Occlusion—Recovery Without Resection. Brit. M. J. **1**:144 (Jan.), 1948.

The incidence of spontaneous recovery is impossible of assessment from data available, as a number of patients, whose cases are undiagnosed and untreated, will recover. The pathology is always one of thrombosis or embolism with severe associated vasospasm. The author reports the case of a 64-year-old retired bank clerk who was seized with severe abdominal colic followed by nausea and vomiting. Examination found him cyanotic with a pulse rate of 120 and a blood pressure of 70/50. There was no rigidity or distention of abdomen, but generalized tenderness was present. A laparotomy was performed. The two upper loops of jejunum were in a condition of hemorrhagic infarction and seemed still viable. The abdomen was closed without intervention. Postoperatively, continuous gastric suction, intravenous fluids, and 50 mg. of heparin, intravenously, every five hours, were given. On the fifth day the patient was quite well and was able to take a normal diet. Heparin was discontinued. The patient made an otherwise uneventful recovery.

WAGNER.

Cox, N.: Cardiac Murmurs in Infancy. Brit. M. J. **1**:148 (Jan.), 1948.

Opinion varies concerning the significance of murmurs heard in infancy. Six hundred thirty ostensibly healthy children enrolled in the Child Health Survey of the Institute of Social Medicine formed the basis of this study. Thirty-two (5 per cent) were found to have systolic murmurs. No diastolic murmurs were heard. Some murmurs were present at the first examination (before the sixth week) and later either disappeared or persisted. Others appeared for the first time at the second or subsequent examination; some of these disappeared or persisted. In twenty-two cases the murmur was not detected until the age of 9 months.

This is a preliminary report on a study which the author plans to continue. These children will be available for observation throughout life, and it is hoped this study will shed light on the significance, progress, and development of these children and their murmurs.

WAGNER.

Steinmann, V. B., Ludi, H., and Barben, H. P.: Circulatory Investigations Resulting From Drugs Which Paralyze the Sympathetic System. I. Ergotamine (Gynergen). Helvet. med. acta **15**:76 (Jan.), 1948.

1. In this study the effect of ergotamine (Gynergen) on the circulation of the healthy human subject was investigated. Ergotamine was administered in varying doses subcutaneously (0.05, 0.1, 0.25, and 0.5 mg.). The changes in the circulatory dynamics were examined after the method of Wezler and Boger dynamics of the heart after the method of Blumberger. Electrocardiograms were registered simultaneously.

2. The following typical effects on the circulation could be shown: slowing of the pulse rate, increase in the diastolic blood pressure, decrease in the pulse pressure, usually a moderate rise in the systolic pressure, small increase in the pulse-wave velocity and the elastic resistance of the elastic cavity organs ("Windkessel") (only with higher doses), and a definite decrease of the buffer factor of the arterial system. Furthermore, the beat and minute output, and sometimes the peripheral resistance were markedly increased. The tension interval was always shortened as was the expulsion interval, the latter, though, to a very moderate degree only. The electrocardiogram showed minor changes in isolated instances only, mostly a flattening of the P wave and a slight increase of the T wave and the conduction interval.

3. The circulatory effect of ergotamine in the human subject shows itself, therefore, to be opposite to that of adrenalin. The fact that in spite of this, both substances can lead to a rise of the arterial pressure-average, is explained on the basis of the observed circulatory changes. It therefore becomes evident that the changes in blood pressure alone do not indicate accurately enough the effects of a circulatory-active substance.

4. Ergotamine acts without doubt peripherally, that is, on the vessels, on the one hand; on the other hand, the great likelihood exists that, up to a certain degree, a direct antiadrenergic action on the heart is also present.

AUTHORS.

Spuhler, V. O., Wiesinger, K. and Meili, E.: Diuretic and Circulating Plasma Volume. Helvet. med. acta **15:**95 (Jan.), 1948.

1. Geigy-blue 536 is suitable for the determination of circulating blood plasma.

2. Our normal values for the circulating plasma volume of 1,800 to 3,800 c.c. correspond to those of the literature.

3. After the administration of Salyrgan the amount of circulating plasma was reduced in every case and the hematocrit was increased in five of six cases. These results may be due to a concentration of blood; this explanation coincides with the assumption that mercurial diuretics have their exclusive site of action in the kidneys and draw water from the blood.

4. Xanthine derivatives have their special site of action in the circulatory system.

5. In some cases of anasarca and diabetes, we observed that the dye disappeared more rapidly than usual from the blood, probably because of a greater capillary permeability. The dye is found regularly in artificial wheals produced by histamine.

AUTHORS.

Makinson, D. H., Olcesky, S., and Stone, R. B.: Vitamin E in Angina Pectoris. Lancet **1:**102 (Jan. 17), 1948.

It has been suggested that vitamin E relieves the pain and improves the exercise tolerance of patients with angina pectoris by its possible action as a coronary vasodilator or by virtue of a beneficial influence on myocardial metabolism.

The authors' series included twenty-two patients (seventeen men and five women), 44 to 66 years of age, who were having frequent attacks of angina. The patients received the following drugs successively: 50 mg. of vitamin E three times daily, phenobarbital, grain ½ three times daily, aminophylline, grains 1½ three times daily, and calcium lactate, grains 5 three times daily (as a control). After each drug had been received for three weeks, the effects were evaluated. The results of this study suggest that vitamin E is no more beneficial than phenobarbital or aminophylline; the authors conclude that vitamin E is not of any therapeutic value in the routine treatment of angina pectoris.

WAGNER.

Godfrey, J.: Thoracic Tenderness in Pulmonary Infarction. New England J. Med. **238:** 86 (Jan. 15), 1948.

Marked, localized intercostal tenderness was observed as an early sign in five cases of pulmonary infarction. None of the cases showed the entire combination of symptoms and signs that generally are considered typical of this condition. It is suggested that chest tenderness in connection with a pleuritic type of pain, in the absence of trauma, be considered suggestive of pulmonary infarction, even in the absence of supporting symptoms, signs, or x-ray changes.

KAY.

Altschule, M. D., and Tillotson, K. J.: Mechanisms Underlying Pulmonary and Cardiac Complications of Electrically Induced Convulsions. New England J. Med. **238:**113 (Jan. 22), 1948.

Maximal forced expiration with extreme diaphragmatic elevation is maintained throughout an electrically induced convulsive seizure. Profuse salivation and excessive bronchial secretion are

accompanying features. In the vigorous inspiration that terminates the seizure, aspiration of this material may result in patchy atelectasis. If this persists and becomes infected, lung abscess may develop. By a similar mechanism, latent tuberculosis may be disseminated.

Rise of peripheral venous pressure was consistently observed. This is attributed to increased intrathoracic pressure. As a result of the rush of impounded blood into the heart in the postconvulsive phase, and because an accumulated oxygen deficit must be overcome, heart work is increased. The myocardial infarctions reported in relation to electric shock therapy probably occur shortly after, rather than during, the convulsion. The authors agree with others that the arrhythmias of the postconvulsive period are probably consequent to vagal reflexes activated by sudden distention of the auricles and great thoracic veins.

D-turbocurarine is recommended to reduce the postconvulsive cardiac strain. Attention is directed to the potentially dangerous vagal stimulating effects of certain other preparations of curare.

KAY.

Crutcher, R. R., and Daniel, R. A., Jr.: Pulmonary Embolism, A Correlation of Clinical and Autopsy Studies. Surgery **23**:47 (Jan.), 1948.

There have been 83,984 admissions to the Vanderbilt University Hospital between 1930 and 1944, inclusive. Four thousand one hundred eighty-two patients (excluding still births) died in the hospital and 2,580 (63 per cent) came to autopsy. There were 35,540 operations (including ear, eye, nose, and throat) carried out during this fifteen-year period. Fifty-five patients had fatal pulmonary emboli, confirmed by autopsy, twenty-five occurring postoperatively. On the basis of 100 per cent autopsies there would have been an expected incidence of thirty-nine cases. Hence, the incidence of fatal pulmonary emboli occurring postoperatively is 0.109 per cent or one in 911 operations.

The authors point out that the incidence of fatal pulmonary emboli is greater in seriously ill patients than in patients who are relatively good risks and whose surgical condition carries a favorable prognosis. In twenty-three of fifty-five autopsy records, thrombi were found in the veins of the pelvis and upper abdomen. There were three cases in which the origin of the emboli was the right side of the heart.

It is pointed out that restriction of activity or fixation of patients in bed is more important than early ambulation as a means of preventing pulmonary emboli. There were 2,107 admissions for pulmonary tuberculosis during this period and although the majority of these patients were confined to bed they were permitted to move about in bed without restriction. There was no instance of fatal pulmonary embolism in this group.

LORD.

Singleton, A. O., and Singleton, A. O., Jr.: Cerebral Hemorrhage Following Repair of A Common Carotid-Internal Jugular Arteriovenous Fistula. Surgery **23**:75 (Jan.), 1948.

The authors discuss fifty cases in the literature of common carotid-internal jugular fistulas, pointing out that seventeen of the patients had restoration of arterial flow while the remaining thirty-three had interruption of the flow by ligation of the common carotid artery. It is of significance that in the group of seventeen patients in whom arterial flow was restored there was only one death, and this was the result of bronchopneumonia. In the group of thirty-three who had arterial interruption, there were three deaths and three recurrences, two deaths having been due to cerebral anemia and one, to coronary occlusion. In addition, one patient had a hemiplegia following ligation of the carotid artery.

The authors report an instance of an arteriovenous fistula between the common carotid artery and internal jugular vein treated by maintainance of arterial continuity and followed by cerebral hemorrhage and death. The patient, a 49-year-old farmer, had been struck in the neck by a rock at the age of 12 years and shortly thereafter had noticed a whirling sound in the head. Three years before his admission, a swelling had appeared in the left side of the neck and for three months the patient had experienced exertional dyspnea and palpatation. Physical examination

revealed the typical signs of an arteriovenous fistula in the left side of the neck and great enlargement of the heart. The operation was carried out under local and cyclopropane anesthesia. The opening in the artery was sutured transvenously and the vein was doubly ligated with excision of the fistula. The patient was returned to the ward in good condition, but four hours postoperatively he could not be aroused and died within one hour. Autopsy revealed the artery in the neck to be intact and there was no evidence of a thrombus. A large hemorrhage had occurred from the left ventriculostriate artery with a large intracerebral blood clot 6 cm. in diameter. In discussion the authors point out that with closure of the fistula the pressure in the carotid artery rose greatly and probably was the cause of the rupture of the intracranial artery.

LORD.

Light, F. P.: A Nine-year Follow-up in Cases of Toxemia of Pregnancy. Am. J. Obst. & Gynec. **55**:321 (Feb.), 1948.

This study is based on a review of the records of 391 women of a total of 530 toxemia clinic patients. Of the 391, thirteen had eclampsia, 275 had mild pre-eclampsia, and 103 had severe pre-eclampsia. The most common residual damage is hypertension. In only a few cases has there been shown to be any renal damage. The study indicated that the duration of the toxemia had little bearing upon the incidence of residual damage. Age, however, is a more important factor. The incidence of residual damage progressively increases with the age of the patient. Among the 103 patients with severe pre-eclampsia, residual damage occurred in forty four (42.5 per cent), whereas residual damage occurred in only seventy (25.4 per cent) of 275 patients with mild pre-eclampsia. The author seriously questions the validity of the assumption that hypertension occurring after toxemia is due to residual damage, but rather feels that it is coincidental essential hypertension manifesting itself.

WAGNER.

Maeck, J. Van S., and Zilliacus, H.: Heparin in the Treatment of Toxemia of Pregnacy. Am. J. Obst. & Gynec. **55**:326 (Feb.), 1948.

In general, the pathologic changes found in women who die from toxemia of pregnancy consist of capillary or arteriolar lesions in different organs, with scattered thrombi in these vessels. Isoagglutination reactions are frequently reported in pregnant patients. Heparin is known to inhibit to some degree the isoagglutination of red blood cells.

A case of pre-eclampsia near term characterized by blurred vision, headache, some edema, and a blood pressure of 170/110 was treated by the continuous intravenous infusion of 150 mg. of heparin in distilled water and 5 per cent dextrose over a period of four and one-half hours. The clotting time rose to eighteen minutes. Following this treatment, the patient showed subjective and objective improvement. Within twenty four hours albuminuria was reduced to a faint trace and the blood pressure, to 140/84. The patient delivered normally thirteen days later.

WAGNER.

Crocket, K. A., and Rhoads, P. S.: Hyperthermia Caused by Penicillin-Heparin in the Treatment of Subacute Bacterial Endocarditis. Ann. Int. Med. **28**:456 (Feb), 1948.

Prolonged hyperthermia of alarming degree accompanied the use of large amounts of penicillin with minimal amounts of heparin in the treatment of a patient with subacute bacterial endocarditis who ultimately recovered as a result of such treatment. The evidence seemed to point toward heparin as the cause of the hyperthermia. This type of unusual reaction to heparin must be remembered since it can make it difficult to determine whether the prolonged fever in a patient with subacute bacterial endocarditis is the result of the disease process or the result of the medication.

WENDKOS.

Prinzmetal, M., Simkin, B., Bergman, H. C., and Kruger, H. E.: Studies on the Collateral Circulation of the Normal Human Heart by Coronary Perfusion With Radioactive Erythrocytes and Glass Spheres. Arch. Inst. de Cardiol. de Mexico **18**:122 (Feb. 20), 1948.

The authors present two new methods for the study of the collateral circulation of the human heart in post-mortem experiments. The first method was based on perfusion by means of red

cells labeled with radioactive phosphorus in suspension in saline solution. Small quantities of radioactive cells can easily be measured by means of Geiger counters or by exposure of the heart to x-ray films for many hours. The second method consisted of the injection of glass spheres of known size through one of the coronary arteries. The spheres were collected at the opposite coronary artery, the coronary sinus, and the ventricular cavities. The diameters of the various anastomoses were thus measured.

After perfusion of one of the branches of the left coronary artery, large amounts of labeled red cells were found in both ventricles. This indicated the existence of numerous anastomoses between the ventricles.

The largest intercoronary anastomoses permitted the passage of spheres of 180 micra and were, therefore, in the arteriolar range. The anastomotic channels between the coronary arteries and either of the ventricular cavities ranged from 70 to 350 micra. They represented arterioluminal and arteriosinusoidal vessels, or Thebesian veins.

The authors conclude that the normal human heart has an extensive collateral circulation with various types of anastomoses. This collateral circulation may function in case of emergency and may enlarge if the pressure gradient is favorable. The evidence shows that collateral circulation does function, in a limited manner, after an acute coronary occlusion. It is not sufficient to prevent an infarct following obstruction of a major coronary artery, but it may limit the size of the infarction.

LUISADA.

Alstad, K. S.: Effect of Thiocyanate on Basal Blood Pressure. Brit. Med. J. **1**: 250 (Feb. 7), 1948.

The author states that many are not convinced of the satisfactory effect of thiocyanates in the treatment of hypertensive disease and refers to a paper by Foster (1943) in which it is stated that there is no evidence of hypotensive effect of thiocyanates in animals, short of a toxic dose.

The author uses (1) casual, (2) basal, and (3) supplemental blood pressures as a means of study and observation. Casual pressure is that recorded after a few minutes' rest in recumbency. Basal pressure refers to pressure recorded when the patient is in a state of basal metabolism (after a night's rest, habituated to surroundings, and so forth). The supplemental pressure refers to the difference between these readings and records the influence of the physical, emotional, and metabolic factors. The author feels that the basal pressure is rather constant in hypertensive patients.

In twenty patients investigated so far, the preliminary investigations indicate that thiocyanates cause a fall in the basal and supplemental pressure compared with the effect of placebos.

The author describes a case demonstrating his point of view. The initial casual pressure at the time of admission for hypertensive encephalopathy was 190/110. The basal pressure next morning was 128/84. At the end of seventeen weeks of therapy the casual pressure was 125/84 and the basal pressure, 88/52. The drug was withdrawn because of diarrhea, which was considered to be toxic, and the blood pressure again rose to initial levels, only to return to optimal levels on administration of the drug again.

The author concludes that a well-marked fall in blood pressure occurs in some patients with essential hypertension following treatment with thiocyanates.

WAGNER.

Schoenewald, G.: Treatment of Angina Pectoris by Reduction of Basal Metabolism. Brit. M. J. **1**: 251 (Feb. 7), 1948.

"From the therapeutic point of view sufferers with angina can be divided into obese, anemic or slim types." The author states that the first two groups are amenable to treatment by reduction of weight and correction of anemia. The third type can be given nitroglycerin either to shorten the attacks or occasionally to prevent them. In connection with the slim type of patient having angina, total thyroidectomy in order to "shed the load" from a failing heart was done with some success fifteen years ago. Today, thiouracil and its derivatives make such major surgery unnecessary.

Three patients with angina pectoris and positive electrocardiographic signs were treated with methylthiouracil. No effort was made to check the basal metabolic rates, as this was considered unnecessary. Their case histories are reported. Relatively large doses (0.6 Gm.) for five to six weeks or more were required before myxedema or relief from angina occurred.

WAGNER.

McKeown, F.: Acute Rheumatism in Pregnancy. J. Obst. & Gynaec. Brit. Emp. **60:** 50, (Feb.), 1948.

"The main purpose of this paper is to report two cases of pregnancy complicated by acute rheumatic heart disease." There was no clinical evidence of the condition in these patients, while the heart showed severe myocardial damage. Brief summaries of the clinical records and of the pathologic reports are given. In short, the patients were well throughout pregnancy, but collapsed and died following delivery. The heart in each instance showed acute rheumatic endocarditis and myocarditis. In retrospect, the hearts of six pregnant patients with mitral stenosis who died from cardiac failure were re-examined and four showed evidence of recent rheumatic myocardial lesions. The author comments as follows: (1) Even in a heart not the site of a mechanical lesion, recurrent rheumatic carditis may be responsible for acute myocardial failure; (2) it is dangerous to correlate the presence of a chronic valvular lesion with fatal outcome in the absence of microscopic examination of the heart.

WAGNER.

Gruhzit, O. M., Fisken, R. A., and Cooper, B. J.: Tetraethylammonium Chloride ($N(C_2H_5)_4NCl$). Acute and Chronic Toxicity in Experimental Animals. J. Pharmacol. & Exper. Therap. **92:**103 (Feb.), 1948.

Tetraethylammonium chloride was administered both orally and parenterally in albino mice, albino rats, and dogs. With large doses, no matter what the route of administration, the animals died within ten to thirty minutes of respiratory failure. The following signs occurred before death: "Severe incoordination, flaccid prostration, respiratory and cardiac depression, marked ptosis and edema of eyelids, mydriasis, ocular muscle paralysis (inversion of eyeballs), erythema of ocular, nasal, and less so of buccal membranes, paralysis of accessory respiratory muscles of chest, and death from respiratory and circulatory collapse."

Sublethal doses were well tolerated when given over long periods of time, even when the amount of drug given was large enough to cause some of these signs two to three hours after administration. During chronic toxicity experiments with sublethal doses, there were no hematologic, renal, or hepatic signs of damage that could be detected by blood counts, total blood nonprotein nitrogen, total plasma protein, albumin-globulin fractions, bromsulphalein blood concentration, or urinalysis.

Necropsy lesions in acute toxicity experiments consisted in "severe congestive blood stasis and petechial hemorrhages in visceral organs, liver, lungs, kidneys, spleen, gastrointestinal tract, urinary bladder, and brain." Edema and necrotic changes were noted around the central veins of the liver. Cloudy swelling was noted in the kidneys, along with changes in the cytoplasm of the cells lining the loops of Henle.

Repeated administration of sublethal doses produced no significant pathologic lesions.

GODFREY.

Lipschitz, W. L., and Stokey, E.: Diuretic Action of Formoguanamine in Normal Persons. J. Pharmacol. & Exper. Therap. **92:**131 (Feb.), 1948.

The authors have previously reported the mode of diuretic action of formoguanamine (J. Pharmacol. & Exper. Therap. **83:**235, 1945).

Formoguanamine has been found to be markedly more effective as a diuretic than urea. Studies on dogs and rabbits failed to reveal any significant toxicity.

Eight healthy male volunteers were given formoguanamine in doses from 3.5 to 11.0 mg. per kilogram of body weight. It was found to give a more consistant diuresis than either caffeine

or theobromine. Both sodium chloride and water excretion were increased. No toxicity was noted among the eight volunteers.

GODFREY.

McNamara, B., Krop, S., and McKay, E. A.: The Effect of Calcium on the Cardiovascular Stimulation Produced by Acetylcholine. J. Pharmacol. & Exper. Therap. **92**:153 (Feb.), 1948.

Acetylcholine causes a pressor response in animals that have been atropinized. This response, in turn, may be blocked by nicotine. The pressor response caused by acetylcholine was believed to be due to ganglionic stimulation; its blockage by nicotine was believed to be due to ganglionic blockage.

The authors showed that by administering calcium they were able to inhibit the ganglionic blocking action of nicotine so that the acetylcholine effect was not abolished. This could be demonstrated both on the intact animal and on the isolated heart. They also demonstrated that calcium potentiates the epinephrine effect upon the heart. They believe that acetylcholine acts directly upon the cardiac musculature by liberating an epinephrine-like substance. The fact that calcium potentiates epinephrine effects and also overcomes nicotine blockage sheds further light on its cardiac effects and the mechanism by which it acts upon the heart.

GODFREY.

Brown, H. S., Allen, E. V., and Craig, W. McK.: The Effect of Tetra-ethyl-ammonium Choloride on Blood Pressure Before and After Sympathectomy for Hypertension. Proc. Staff Meet., Mayo Clin. **23**:94 (Feb. 18), 1948.

Nine subjects who failed to obtain an entirely satisfactory reduction of the blood pressure from transdiaphragmatic or infradiaphragmatic sympathectomy were investigated. When tetraethylammonium chloride was given intravenously after postoperative periods of from two weeks to four years, the blood pressure of eight of the nine subjects was temporarily reduced to normal. In the ninth case, exceptional because of nephrectomy as well as sympathectomy, the blood pressure actually increased following the injection. The blood pressure of only one of six patients tested preoperatively was reduced to normal.

The authors feel that these observations suggest that hypertension which persists after sympathectomy is not due to organic changes which affect the lability of the arterioles. They explain the difference in the blood pressure response after sympathectomy as being the result either of an increased susceptibility of the arterioles to the drug or of a more complete block of the remaining ganglia by the drug following sympathectomy. These observations may be a clue to the genesis and treatment of hypertension.

ARKLESS.

Wegria, R., and Boyle, M. N.: Correlation Between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma. Am. J. Med. 4:373 (March), 1948.

The authors have attempted to correlate the concentration of quinidine in the plasma and in the heart and the intensity of the effect of quinidine on the heart.

The first part of the experiment consisted of ten studies on six patients to correlate the plasma concentration of quinidine and the intensity of the effect of quinidine on the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. Single and/or repeated oral doses of quinidine sulfate were given patients with chronic auricular fibrillation. The intensity of cardiac effect of the drug and its plasma concentration were found to be grossly parallel, but not parallel in a strictly quantitative manner. Discrepancies were found in that the plasma level of the drug decreased faster than the intensity of its cardiac effect.

The second part of the experiment involved the determination of the concentration of quinidine in the plasma and heart muscle of dogs given the drug orally. These experiments showed that the concentration of quinidine in the tissues is much higher then the plasma concentration. The peaks of tissue and plasma concentration correspond as far as time is concerned.

The authors believe that if the results of the experiments performed on dogs are applicable to man, the main factor accounting for the discrepancies between quinidine plasma concentration and intensity of the effect on the heart is the fact that the cardiac effect is not proportional either to the plasma or to myocardial concentration of the drug. It would appear that a further increase in the heart concentration yields a diminished increment of cardiac effect.

WOODS.

Grayson, C. E.: Cardiac Calcifications, Annular and Valvular (Leaflet). California Med. **68**:121 (March), 1948.

A brief discussion of calcareous deposits in the aortic and mitral annulus and in the valve leaflets is presented. The average age of women with calcifications is consistently greater than that of men except in the group with calcifications of the aortic ring. The average age of patients having ring calcifications is greater than the age of those having leaflet calcifications. If the group with both aortic ring and mitral ring calcifications is combined with the group having isolated calcifications of the aortic ring, the average age difference becomes still greater. The average age of patients having mitral leaflet calcifications is considerably lower than the average age of those with calcifications in the mitral annulus.

The incidence of hypertension is higher in those patients having mitral or aortic and mitral ring calcifications. The association of other visible calcifications in the arteries and in the bronchi is also higher in these groups. The lack of abnormal electrocardiographic findings in patients with aortic calcifications of slight or moderate degree and in patients with mitral ring calcifications is consistent with the lack of effect of these lesions upon the heart function. The incidence of a rheumatic fever history is considerably higher in those with leaflet calcifications.

Aortic ring calcifications may occur in association with heart disease or it may be incidental to other visceral disease. Calcifications in the mitral annulus fibrosus are probably of less clinical importance than calcification in the aortic ring. Mitral annulus deposits can be entirely unsuspected until the patient is fluoroscoped. Small mitral leaflet calcifications are distinguished from calcifications of the ring by their snapping motion and by the more localized extent of the deposit.

It seems clear that the deposits of calcium are due to more than one disease process. The annular type occurs in older people and is probably related to an atherosclerotic process. The leaflet type occurs in younger people and is probably related to rheumatic heart disease. Since fluoroscopy permits distinction between annular and leaflet calcification, one has an additional aid in distinguishing rheumatic from nonrheumatic heart disease.

BELLET.

Kempner, W.: Treatment of Hypertensive Vascular Disease With Rice Diet. Am. J. Med. **4**:545 (April), 1948.

The article is one of a series of seminars on hypertension and summarizes the author's experience with the use of the rice diet in 500 patients with hypertensive vascular disease. It is stated that the diet has been ineffective in 178 patients while it proved beneficial in 322 as judged by production of one or more of the following effects: decrease in "mean" arterial blood pressure of at least 20 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; a change in T_1 of the electrocardiogram from completely inverted to upright; and disappearance of severe retinopathy. Subjective improvement has not been accepted as evidence of successful therapy. Whether the effect of the diet is due to its low sodium content, low cholesterol content, or other factors is as yet unsettled.

The regimen is described in detail, and indications and contraindications are given. Data are presented to show that protein equilibrium, hemoglobin, and plasma proteins are maintained, while hypercholesterolemia decreases markedly on the diet. There is a decrease of sodium and chloride concentration in urine and serum and a decrease in excretion of chloride, sulfate, and ammonia in the urine.

WOODS.

Ross, R. A., Lambeth, S. S., Thomas, W. L., and Carter, F. B.: Fifty-Four Deaths Occurring in Pregnant Patients Who Had Hypertension. Am. J. Obst. & Gynec. 55:591 (April), 1948.

The material consisted of fifty-four patients who died in the immediate puerperium or in pregnancy and who had a blood pressure higher than 140/90. There were only seventeen living children from the fifty-four dead mothers. An elevated diastolic pressure was the common denominator of all patients. Many of the patients were colored, and previous histories regarding hypertension were unknown in twenty-five of the fifty-four cases. Most of the patients were over 30 years of age. The average number of previous pregnancies was 5.8; the average number of living children was 4.6. Changes in the optic fundi, such as thinning of vessels, increased light reflex, tortuosity, and a-v nicking, were present in thirty-eight cases. A total of twenty-five patients were thought to have enlarged hearts, and thirty-three of forty-six patients were overweight.

The authors conclude that the hypertensive woman with enlarged heart, changes in optic fundi, and albuminuria has a poor prognosis when pregnant. Serious consideration of interruption by the most conservative means should be given such patients, regardless of the stage of pregnancy, and contraceptive measures should be suggested.

WAGNER.

Blumgart, H. L., and Altschule, M. D.: Clinical Significance of Cardiac and Respiratory Adjustments in Chronic Anemia. Blood 3:329 (April), 1948.

The status of the cardiorespiratory system and the related manifold compensatory mechanisms which provide a maximal supply of oxygen to the tissues in the presence of anemia are discussed.

In chronic anemia, when the oxygen-carrying capacity of the blood is diminished, an adequate supply to the tissues is maintained by an increased cardiac output, an increased velocity of blood flow, and a relatively more complete abstraction of oxygen from the blood as it passes through the capillaries. Related to the increased blood flow is a decrease in peripheral resistance, but it is not uniform, resulting at times in a reduced blood flow in the hands and feet while the blood flow of other parts of the body is increased. The metabolic rate is not strikingly altered. The blood volume is generally slightly reduced but the plasma volume is normal. The deviations from the normal values vary from patient to patient, but generally are definite when the hemoglobin values are less than 50 per cent and are greatest at the lowest levels of hemoglobin concentration.

Changes in respiration favor the occurrence of exertional dyspnea. These changes are: an increased respiratory minute volume, a decreased vital capacity including the reserve and complemental air volumes and an increased residual air. Abnormalities in carbon dioxide transport and dissociation, reduced arterial oxygen capacity, and decreased blood oxygen saturation during effort, together with the frequently observed elevated blood lactic acid values, are noted.

The clinical manifestations of chronic anemia include cardiovascular and respiratory symptoms and signs. The cardiac manifestations include palpitation and dyspnea on exertion, tachycardia, cardiac enlargement, murmurs, and electrocardiographic changes. It is observed that the arterial blood pressure is frequently lowered while the venous pressure is generally within the limits of normal. The occurrence of angina pectoris and congestive failure in some patients with the development of anemia, and their disappearance as the anemia is alleviated, is discussed.

The problem of differentiating the concomitant occurrence of exertional dyspnea, edema, and hepatomegaly in severe anemia from their occurrence in myocardial insufficiency presents itself. Aid is derived from the absence of venous engorgement and orthopnea in anemia; the absence of cyanosis cannot be relied upon since cyanosis cannot occur if the patient has less than 5 grams per cent of hemoglobin.

BEIZER.

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CONFERENCE OF LOCAL HEART ASSOCIATIONS DISCUSSES COMMUNITY PROGRAMS AND COOPERATION IN 1949 NATIONAL CAMPAIGN

Presidents and chairmen of the governing boards of affiliated local heart associations and representatives from many states and cities interested in forming new local heart associations attended a special conference at the Hotel Plaza, New York, on September 24, under the auspices of the American Heart Association. The purpose of the conference was to discuss plans for the development of new community programs to combat heart disease through the creation of additional heart associations as well as the strengthening of existing associations.

A preview of plans for the Association's 1949 national educational and fund-raising campaign was presented to the conference along with suggestions for local participation. It was announced that Harold Stassen had accepted the post of National Campaign Chairman, heading a National Campaign Planning Committee composed of such prominent figures as Winthrop Aldrich, Chairman, Chase National Bank of the City of New York, who will serve as Campaign Treasurer; Colby M. Chester, Honorary Chairman of General Foods Corporation; Henry R. Luce, Publisher, Time Magazine; Charles E. Wilson, President, General Motors Corporation; and Mark Woods, President, American Broadcasting Company.

Under the chairmanship of Thomas I. Parkinson, President, Equitable Life Assurance Society, an even more extensive list of prominent Americans comprising the National Sponsors Committee for the forthcoming campaign was announced. These include Albert B. Chandler, Baseball Commissioner; Dr. James B. Conant, President, Harvard University; Gardner Cowles, President and Editor, Look Magazine; Walter S. Gifford, Chairman, American Telephone and Telegraph Company; Tom M. Girdler, Chairman, Republic Steel Corporation; William Green, President, American Federation of Labor; Phillip Murray, President, Congress of Industrial Organizations; Herbert H. Lehman, former Governor of New York; Elmo Roper; Niles Trammel, President, National Broadcasting System; and Owen D. Young, Honorary Chairman, General Electric Company.

A. W. Robertson, Chairman of the Board of the Association, emphasized the need for new local affiliates to direct and coordinate community services for cardiac patients so that the latest advances of medical research may be brought swiftly to the individual in his own community. Dr. Charles A. R. Connor, Medical Director of the Association, introduced to the conference delegates the newly published "Program Guide for Local Heart Associations." He explained that the purpose of the booklet, which has been distributed to all affiliates of the Association, is to present a broad framework for local programs adaptable to meet specific community needs. Dr. Connor said the Association hoped eventually to have an enlarged field staff to assist in the organization of local affiliates and in the development of local programs.

Dr. Connor announced that the recently organized National Conference of Executive Secretaries of local heart associations would meet in New York on October 19 and 20. The purpose of this group is to serve in an advisory capacity concerning the needs and requirements of local affiliates and the implementation of American Heart Association policies with reference to community programs.

Dr. T. Duckett Jones, Member of the Board of Directors of the Association, reviewed the recently published booklet outlining policies adopted by the Assembly last June. Dr. Jones emphasized the need for a strong national organization to assist in the development of community programs. He pointed out that the policies of the Association were designed to aid in the

organization of additional cardiac services and facilities throughout the entire country, the planning of preventive measures, the application of scientific knowledge, and the correlation of existing agencies. Dr. Jones urged local associations to develop a carefully planned and integrated program, with emphasis on improved service to the individual. Such a program, he said, may require many years to develop, but it should encompass the entire field of cardiovascular disease and should be adapted to the needs of various areas.

Dr. H. M. Marvin, President-Elect of the Association, summarized the "Recommendations From the Research Policy Committee" which state that "the ultimate aim is to develop a continuing program of productive research . . . over the country as a whole, rather than in a few centers only." The recommended program will include the training and support of career investigators in the field of cardiovascular disease, research fellowships, and the provision of grants for approved research projects. To develop the program, a Research Allocations Committee is to be elected by the Scientific Council of the Association.

Dr. G. K. Fenn acted as Chairman at the morning session, while Mr. Robertson presided over the afternoon session, which concentrated on fund-raising and promotional plans for the 1949 National Campaign.

E. J. Ade, the Association's Fund-Raising Director, outlined campaign organizational procedures and methods of fund-raising. Mr. Ade explained that a goal of $5,000,000 had been decided upon for the 1949 campaign on the basis of a study of what the Association, in its present state of development, could accomplish with that amount. Discussing the services which the National Campaign Headquarters would render for local cooperating groups and affiliated associations, Mr. Ade mentioned leadership and guidance in campaign planning, fund-raising assistance, and a national publicity and educational program.

Mr. Ade exhibited the Plastic Heart coin bank which will again be available as a fund-raising device, and a new "Save-a-Heart" bank for smaller contributions. He said that a Campaign Chairman's Handbook, containing specific suggestions for local organization and promotion, will be distributed shortly.

M. Frederick Arkus, of Win Nathanson Associates, public relations counsel for the Association, presented the basic public relations objectives of the forthcoming campaign. These include education of the public about the problem of heart disease and the accomplishments of science, identification of the Association in the public consciousness in order to win acceptance and support, and laying of the groundwork for the development of local heart associations and community programs. Mr. Arkus outlined plans for the national publicity program, which will support local efforts, through all media of information, including national wire services, syndicates, magazines, radio, television, and motion pictures. He also illustrated the type of campaign posters and educational pamphlets which will be distributed to local groups.

Among those attending the conference were representatives from Chicago, New York, Philadelphia, St. Louis, Kansas City, New England, Ohio, New Jersey, Florida, Texas, Louisiana, Wisconsin, Minnesota, and Maryland.

As the American Heart Journal went to press, the National Campaign Planning Committee and the National Sponsors Committee were still in the process of formation. The following are the names of those who had already accepted membership on these campaign committees:

MEMBERS OF NATIONAL CAMPAIGN PLANNING COMMITTEE

NAME	TITLE	COMPANY	CITY
Winthrop W. Aldrich	Chairman	Chase National Bank of the City of New York	New York
John Ballantyne	Chairman	Philco Corporation	Philadelphia
David T. Beals	President	The Inter-State National Bank	Kansas City, Mo.
James B. Black	President	Pacific Gas & Electric Co.	San Francisco
Colby M. Chester	Honorary Chairman	General Foods Corporation	New York
S. DeWitt Clough	Chairman	Abbott Laboratories	North Chicago
William E. Cotter	Counsel	Union Carbide & Carbon Corporation	New York
Emerson Foote	President	Foote, Cone & Belding	New York

MEMBERS OF NATIONAL CAMPAIGN PLANNING COMMITTEE—Continued

NAME	TITLE	COMPANY	CITY
Walter D. Fuller	President	The Curtis Publishing Co.	Philadelphia
Maurice Goldblatt	Chairman	Goldblatt Bros., Inc.	Chicago
J. L. Holloway	President	Crane Co.	Chicago
Honorable J. K. Javits	Member	House of Representatives, Congress of the United States	Washington, D. C.
Dr. Robert L. Johnson	President	Temple University	Philadelphia
T. Duckett Jones, M.D.		The Helen Hay Whitney Foundation	New York
James K. Lochead	President	American Trust Company	San Francisco
Henry R. Luce	Editor and Publisher	Time Magazine	New York
John A. McCone	President	Joshua Hendy Corporation	Los Angeles
Max McGraw	President	McGraw Electric Company	Chicago
Robert L. Mehornay, Sr.	President	North-Mehornay Furniture Company	Kansas City, Mo.
Arthur W. Page			New York
Thomas I. Parkinson	President	Equitable Life Assurance Society	New York
Alan M. Scaife	Vice-President	T. Mellon & Sons	Pittsburgh
E. T. Stannard	President	Kennecott Copper Corporation	New York
Herman W. Steinkraus	President	Bridgeport Brass Company	Bridgeport
John A. Stevenson	President	The Penn Mutual Life Insurance Company	Philadelphia
Arthur Hays Sulzberger	Publisher	The New York Times	New York
Frederick K. Trask, Jr.	Partner	Payson & Trask	New York
Cloud Wampler	President	Carrier Corporation	Syracuse
Charles E. Wilson	President	General Motors Corporation	Detroit
Mark Woods	President	American Broadcasting Co., Inc.	New York
Irving S. Wright, M.D.			New York

MEMBERS OF NATIONAL SPONSORS COMMITTEE

NAME	TITLE	COMPANY	CITY
Nathan Adams	Chairman	First National Bank in Dallas	Dallas
General Julius Ochs Adler		The New York Times	New York
William B. Bell	President	American Cyanamid Company	New York
Seymour Berkson	General Manager	International News Service	New York
Lindsay Bradford	President	City Bank Farmers Trust Company	New York
Morgan B. Brainard	President	Aetna Life Insurance Company	Hartford
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